EFFORTS TOWARDS THE TOTAL SYNTHESIS OF BREVENAL AND DEVELOPMENT OF OLEFINIC AMIDE AND OLEFINIC LACTAM CYCLIZATIONS USING A REDUCED TITANIUM ALKYLIDENE

by

Jie Zhou

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STATEMENT OF DISSERTATION APPROVAL

The dissertation of **Jie Zhou**

has been approved by the following supervisory committee members:

Jon D. Rainier	, Chair	**08/26/2010** Date Approved
Gary E. Keck	, Member	**08/26/2010** Date Approved
Cynthia J. Burrow	, Member	**08/26/2010** Date Approved
Haitao(Mark) Ji	, Member	**08/26/2010** Date Approved
David P. Goldenberg	, Member	**08/26/2010** Date Approved

and by **Henry S. White** , Chair of the Department of **Chemistry**

and by Charles A. Wight, Dean of The Graduate School.

ABSTRACT

Brevenal and its dimethyl acetal were isolated from laboratory cultures of the dinoflagellate *Karenia brevis* by Barden and co-workers in 2005. Brevenal has the potential to serve as therapeutic agents for the treatment of brevetoxins poisoning because of their low toxicity and ability to block the effect of brevetoxins in vivo. This dissertation describes our efforts towards the total synthesis of brevenal. A C-glycoside/metathesis approach is used in our synthesis. Of note is the generation of α-C-glycosides in one pot by using a DMDO oxidation and zinc mediated C-C bond formation sequence. Lewis acid TBSOTf is very important in these reactions. Nucleophiles prefer to add from the axial position regardless of the epoxides.

Cyclic enamides are valuable in their own and interesting precursors to a variety of natural products containing nitrogen. Although the olefinic-amide cyclizations would be synthetically useful, there are few reports of related cyclization that employ amides. Described here is the use of a reduced Titanium alkylidene reagent to effect one-step olefinic-amide and olefinic-lactam cyclizations.

To my parents for their unconditional love and support

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LIST OF ABBREVIATIONS

[α]	specific rotation [expressed without units; units, deg mL/(g·dm), are understood]
Ac	acetyl
AcOH	acetic acid
AIBN	2,2'- Azobisisobutyronitrile
APCI	Atmospheric pressure chemical ionization
appt	apparent (spectral)
atm	atmospheres (pressure)
Boc	*tert*-butoxycarbonyl
Bn	benzyl
br	broad (spectral)
Bu	butyl
t-Bu	*tert*-butyl
Bz	benzoyl
^{o}C	degrees Celsius
calcd	calculated
CI	chemical ionization (in MS)
cm	centimeter

CuTC	copper(I)-thiophene-2-carboxylate
CSA	10-camphorsulfonic acid
d	day, doublet (spectral)
DBU	1,8-diazabicyclo[5.4.0] undec-7-ene
DCC	dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de	diastereomeric excess
DIBAL-H	diisobutylaluminum hydride
DMA	dimethylacetamide
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DMF	N,N-dimethylformamide
DMS	dimethyl sulfate
DMSO	dimethyl sulfoxide
ee	enantiomeric excess
equiv	equivalents
Et	ethyl
EtOAc	ethyl acetate
EI	electron impact
FAB	fast atom bombardment
g	gram
h	hour
HMPA	hexamethylphosphoramide

Hunig’s Base	diisopropylethylamine
HRMS	high-resolution mass spectrum
Hz	Hertz
IC_{50}	50% inhibitory concentration
IR	infrared
J	coupling constant (in NMR)
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
m	multiple (spectral)
M	moles per liter
*m*CPBA	*m*-chloroperoxybenzoic acid
m/z	mass to charge ratio (in MS)
MHz	megahertz
min	minute
mol	mole
MOM	methyoxymethyl
mp	melting point
MS	mass spectrometry
NBS	N-bromosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	Nuclear magnetic resonance
nOe	nuclear Overhauser effect

Ns	4-nitrobenzenesulfonyl
PCC	pyridinium chlorochromate
Ph	phenyl
PMB	p-methoxybenzyl
ppm	parts per mollion (in NMR)
PPTS	pyridinium p-toluenesulfonate
i-Pr	isopropyl
Pyr	pyridine
q	quartet
R_f	retention factor (in chromatography)
RCM	ring closing metathesis
rt	room temperature
s	singlet or second
t	triplet
TBAF	tetrabutylammonium fluoride
TBDMS	*t*-butyldimethylsilyl
TBDPS	*t*-butyldiphenylsilyl
TEA	triethylamine
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran

TIPS	triisopropylsilyl
TMEDA	N,N,N’,N’-tetramethylethylene diamine
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthanate
Ts	*p*-toluenesulfonyl
TsOH	*p*-toluenesulfonic acid
VGSC	voltage gated sodium channels

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CHAPTER 1

EFFORTS TOWARDS THE TOTAL SYNTHESIS OF BREVENAL

Introduction

Marine polycyclic ether natural products have been interesting synthetic targets for years because of their unique and highly complex structures in addition to their diverse and potent biological activities.[1-3] Since the discovery of brevetoxin B in 1981,[4] a number of bioactive polyether compounds have been isolated from the marine dinoflagellate *Karenia brevis*, the organism responsible for the toxic red tides along Florida's Gulf Coast.[5] The most well-known of these are the brevetoxins, which consist of three different structural backbones: brevetoxin B (Figure 1.1), brevetoxin A (Figure 1.2) and hemibrevetoxin B (Figure 1.3).

PbTx-2 (**1.1**), R = $CH_2C(=CH_2)CHO$
PbTx-3 (**1.2**), R = $CH_2C(=CH_2)CH_2OH$
PbTx-5 (**1.3**), K-Ring acetate
PbTx-6 (**1.4**), H-Ring epoxide
PbTx-8 (**1.5**), R = CH_2COCH_2Cl
PbTx-9 (**1.6**), R = $CH_2CH(CH_3)CH_2OH$

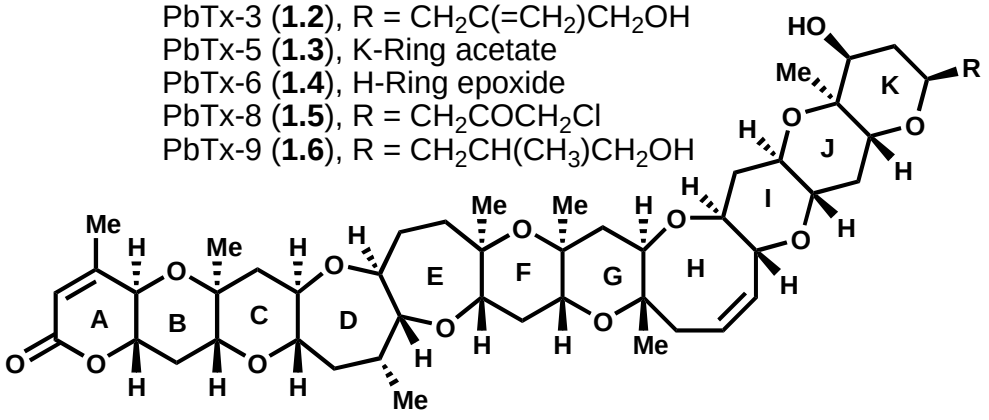


Figure 1.1. Structure of brevetoxin B backbone

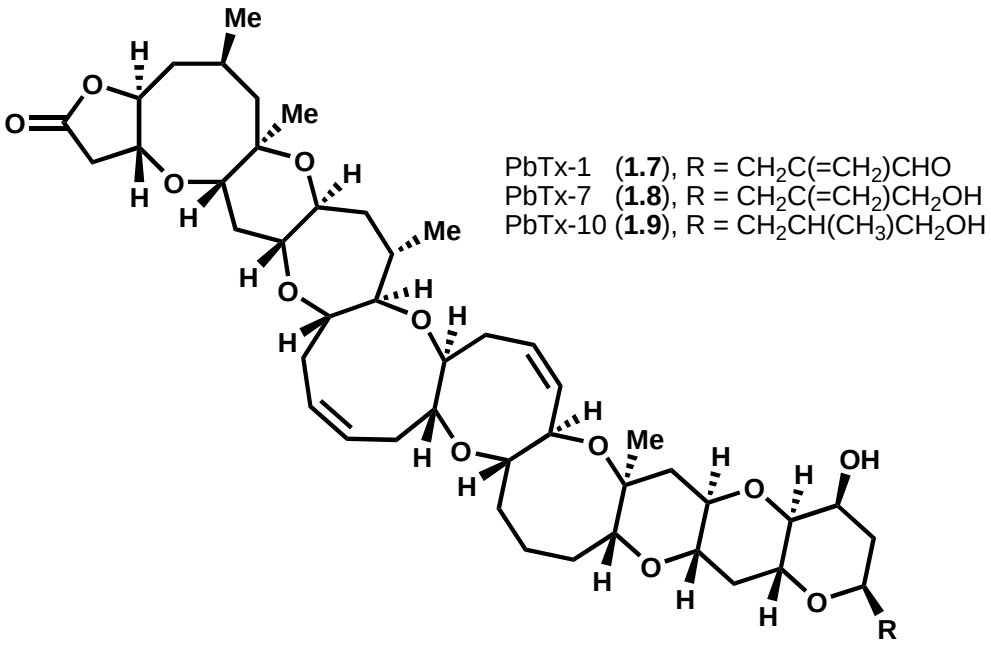


Figure 1.2. Structure of brevetoxin A backbone

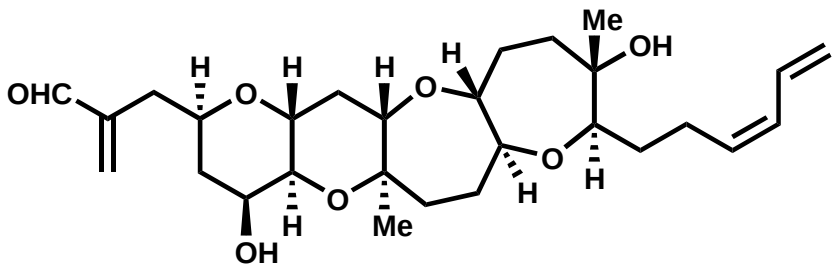


Figure 1.3. Structure of hemibrevetoxin B

Brevetoxins A and B bind with high affinity to site 5 of voltage gated sodium channels (VGSC) in neurons. Orientation of the brevetoxins is believed to be in a head-down with the A-ring lactone facing the cell interior and the tail end of the molecule facing outward.[6]

Voltage gated sodium channels are ion channels. Ion channels are integral membrane proteins that permit the passage of ions based solely on their charge and size. The archetypal channel pore is just one or two atoms wide at its narrowest point and is selective for specific species of ions, such as sodium or potassium. Ions move through the channel pore single file nearly as quickly as the ions move through free fluid. Passage through the pore is governed by a gate which may be opened or closed by chemical or electrical signals, temperature, or mechanical force, depending on the type of channel.

Ion Channels are classified according to the trigger that opens the channel for such ions in eukaryotes. Sodium channels are responsible for the passage of sodium ions through a cell's plasma membrane and consist of a large α subunit that associates with other proteins, such as β subunits. An α subunit forms the core of the channel and is functional on its own. It has four repeat domains, labeled I through IV, each containing six membrane-spanning regions, labeled S1 through S6. Binding of brevetoxins A and B to tissues containing VGSC results in membrane depolarization, repetitive firing, and increased sodium currents.[7-10] Further experiments indicate that brevetoxins A and B activate VGSC by prolonging their mean open time, inhibiting channel inactivation, and shifting the channel activation potential to more negative values. Humans are most commonly affected by brevetoxins that have been aerosolized in sea spray or that have

bioaccumulated in shellfish. Inhaled brevetoxins cause respiratory irritation and breathing difficulties in sensitive populations.[11-13]

Gambierdiscus toxicus is another important dinoflagellate. It produces a number of ladder like polycyclic ethers such as ciguatoxin **1.11** (Figure 1.4), maitotoxin **1.12** (Figure 1.5), gambierol **1.13** (Figure 1.6), gambieric acids **1.14-1.17** (Figure 1.6) and yessotoxin **1.18** (Figure 1.6).

Ciguatera, the most widespread seafood poisoning event, is caused by the ingestion of coral reef fish that have become toxic through their diet.[14] The main responsible toxins are thought to be the ciguatoxins and maitotoxin. The clinical symptoms are diverse.[15] Neurologic disturbances are prominent. Reversal of thermal sensation is one of the most characteristic symptoms of ciguatera. Other illnesses included prostration, cyanosis, erethism and joint pain.

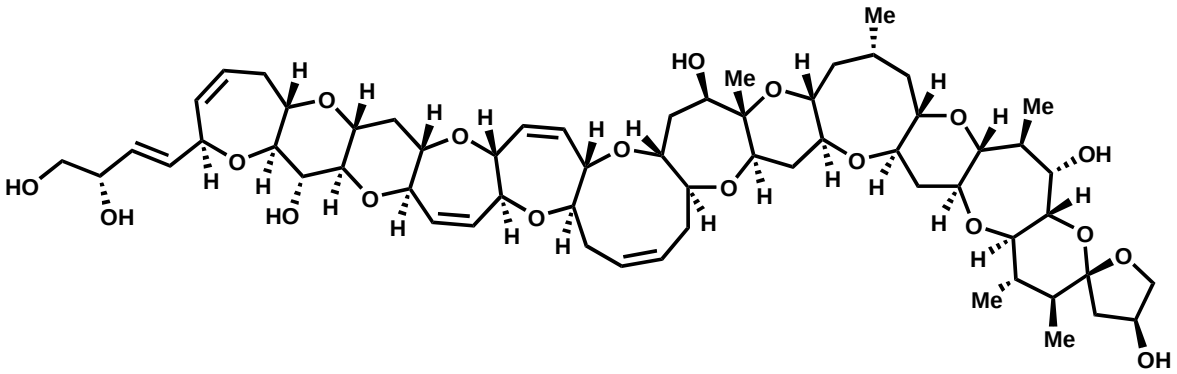


Figure 1.4. Structure of ciguatoxin

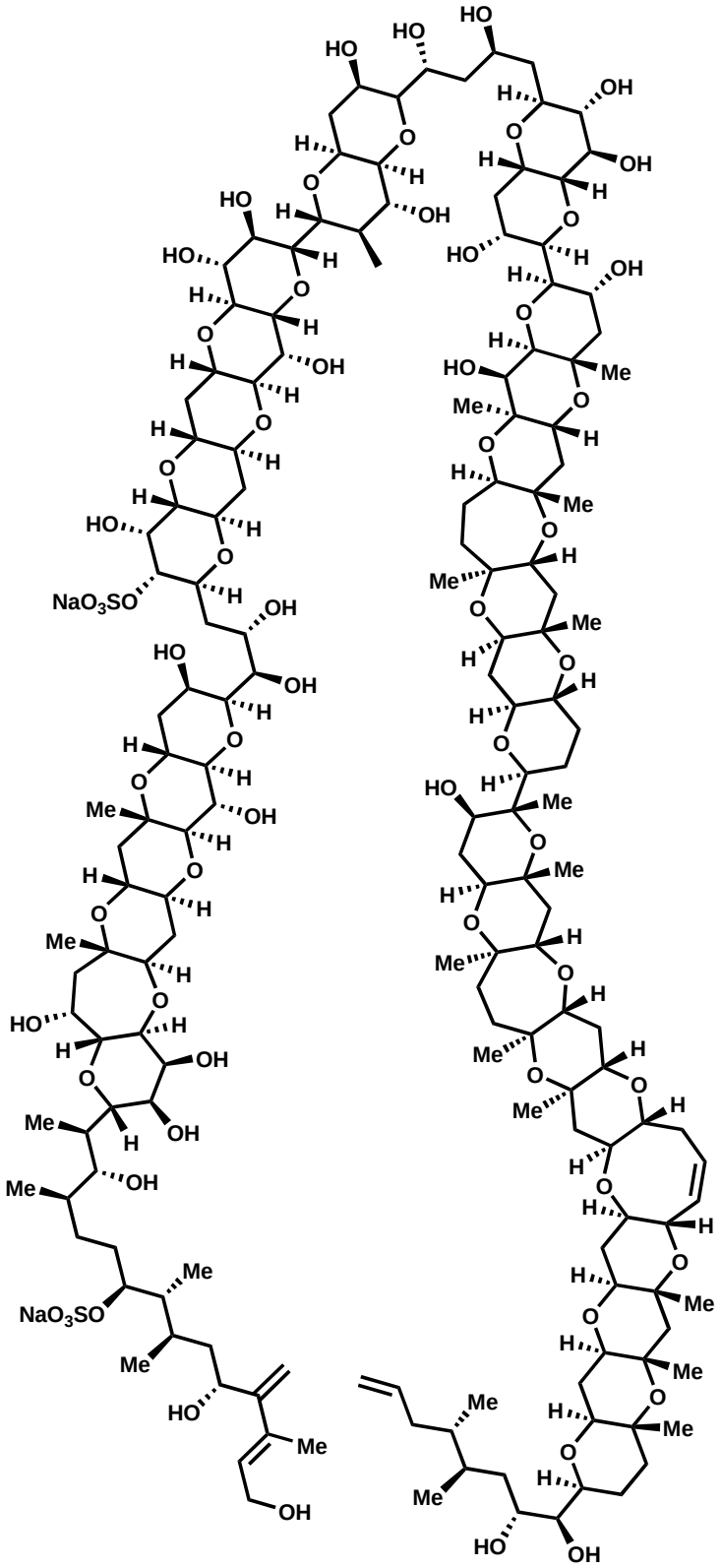
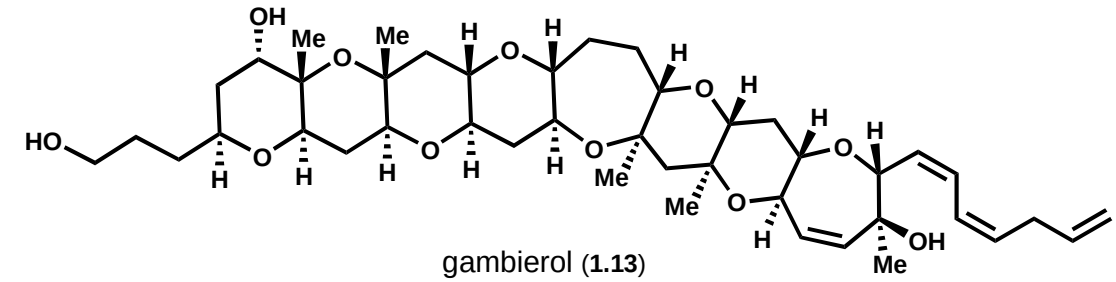
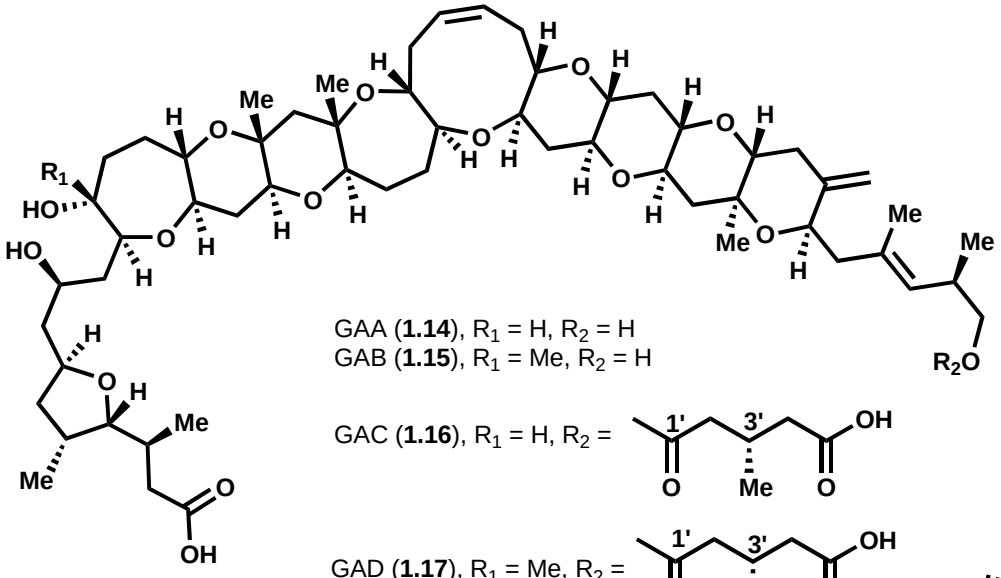


Figure 1.5. Structure of maitotoxin



gambierol (**1.13**)



GAA (**1.14**), R_1 = H, R_2 = H
GAB (**1.15**), R_1 = Me, R_2 = H

GAC (**1.16**), R_1 = H, R_2 =

GAD (**1.17**), R_1 = Me, R_2 =

yessotoxin (**1.18**)

Figure 1.6. Structures of gambierol, gambieric acids and yessotoxin

Ciguatoxin was first isolated by Scheuer's group at University of Hawaii[16] and the structure was elucidated by Yasumoto's group in 1989.[17] Ciguatoxin was found in both the dinoflagellate *Gambierdiscus toxicus* and in toxic fish. Ciguatoxins target the VGSCs in a similar fashion to the brevetoxins, but their binding affinities are 25- to 400- fold stronger.[18]

Maitotoxin, the largest nonpolymeric natural product, has a molecular weight of 3422 Daltons (as the disodium salt, $C_{164}H_{256}O_{68}S_2Na_2$). It contains 32 rings, 98 stereogenic centers and one trisubstituted double bond. Maitotoxin was first isolated from the gut of the surgeon fish *Ctenochaetur striatus*[19] and later from the dinoflagellate *Gambierdiscus toxicus.*[20] Maitotoxin has extremely potent bioactivity. The lethality against mice (LD_{50} is 50 ng/kg) suggests that it is the most potent nonproteineceous toxin.[21] Maitotoxin was found to increase Ca^{2+} influx which could be blocked by verapamil, suggesting that maitotoxin acts on a voltage-sensitive Ca^{2+} channel.[22] The Ca^{2+} flux induced by maitotoxin leads to secondary effects such as muscle contractions, stimulation of hormones/neurotransmitter release, activation of phospholipases C and A2 and activation of protein kinases.[23]

Gambierol is another polyether isolated from the dinoflagellate *Gambierdiscus toxicus* by Yasumoto and co-workers in 1993.[24] It shows toxicity against mice with a LD_{50} of 0.6 μg/Kg. The symptoms that result from gambierol resemble those shown by ciguatoxins, inferring the possibility that it is also implicated in ciguatera.[25] Synthetic gambierol from our laboratory has helped in the understanding of the interactions between gambierol and VGSC. In collaboration with Tom Murray and co-workers, gambierol was found to inhibit the binding of PbTx-2 to site 5 of VGSC and act as a

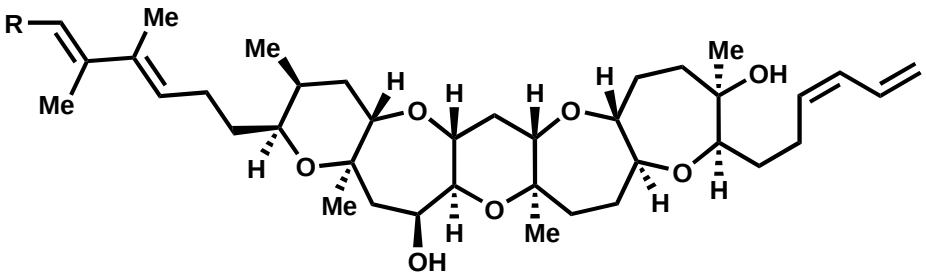
competitive antagonist of PbTx-2.[26(a)] In collaboration with Jan Tytgat and Dirk Synders, we found that gambierol is a low nM antagonist of voltage gated potassium channels and that it does not bind to VGSCs.[26(b)] In collaboration with Murray, we have also demonstrated that gambierol does not elicit a neurotoxic response.[26(a)]

Other important compounds from *Gambierdiscus toxicus* include the gambieric acids. The gambieric acids have displayed strong antifungal activity with inhibitory activity against *Aspergillus niger* that was 2000 times greater than that of amphotericin B.[27] A further study by Yasumoto and Hirama showed that gambieric acid A competitively inhibits the binding of isotope-labeled dihydro-brevetoxin ([^{3}H]PbTx-3) from the VGSC of rat brain synaptosomes.[25]

Diarrhetic shellfish poisoning (DSP) is widely distributed over the world, particularly in Japan and the northwestern part of Europe.[28] It is associated with eating bivalves such as mussels, scallops or clams which have accumulated dinoflagellate toxins. Yessotoxin was isolated from the scallop *Patinopecten yessoensis* in Japan.[29] It was found to induce apoptosis through a mitochondrial signal transduction pathway.[30] Both yessotoxin and its disulfated counterpart bind to the transmembrane domain of glycophorin A and cause the dissociation of oligomers of the protein.[30]

Isolation and bioactivities of brevenal

In 2005, a new polyether natural product named brevenal (Figure 1.7) was isolated from laboratory cultures of *Karenia brevis* together with its dimethyl acetal derivative by Baden and co-workers.[31] More recently, these compounds have also been found in extracts of natural red tide blooms from both the east and west coasts of Florida.



brevenal (**1.19**): R = CHO
brevenal dimethyl acetal (**1. 20**): R = $CH(OMe)_2$

Figure 1.7. Initial structure of brevenal and brevenal dimethyl acetal

The presence of brevenal has been found to vary with the phase and toxicity of the bloom.[32] Brevenal and its dimethyl acetal derivative contain five fused cyclic ether rings and a structural backbone that is different from both the brevetoxins and hemibrevetoxin B. The arrangement of the 6, 7, 6, 7, 7 ether rings in brevenal is unique among dinoflagellate metabolites.

The interactions between brevenal and VGSC were evaluated by using a rat brain synaptosome receptor-binding assay. Brevenal and its dimethyl acetal were found to inhibit [^{3}H]-PbTx-3 binding in a concentration-dependent manner.[31] Similar antagonistic activity against brevetoxins' binding to VGSC has also been observed for synthetic gambierol[26] and gambieric acid A.[25]

The antagonistic effects of brevenal and brevenal acetal on brevetoxin toxicity were tested using a fish bioassay. Brevenal shows no toxicity at micromolar concentrations while brevetoxins are lethal in nanomolar concentrations. In addition, Fish exposed to a combination of brevenal and PbTx-2 survived longer than those exposed to PbTx-2 alone. This result suggests that brevenal can delay brevetoxin-induced mortality in fish.[31] When brevenal dimethyl acetal was used instead of brevenal, the delay of

mortality did not achieve statistical significance. The "anti-toxin" properties of brevenal were further explored by Abraham and co-workers in sheep models. Their study shows brevenal can block bronchoconstriction caused by the inhalation of the brevetoxins. They also found that brevenal increases mucociliary clearance at a 10^{-6} lower concentration when compared to amiloride.[33] Amiloride is currently used to treat cystic fibrosis which is caused by a mutation in the gene for the protein cystic fibrosis transmembrane conductance regulator.[33]

Thus, brevenal and its derivative have the potential to serve as therapeutic agents for the treatment of brevetoxin poisoning because of their low toxicity and ability to block the effects of the brevetoxins *in vivo*. Because of this and an interest in better understanding the ion channel binding properties of the ladder toxins, we initiated a program targeting the synthesis of brevenal and derivatives. Thus, following a brief discussion of other work targeting brevenal is a detailed discussion of our work.

Sasaki's total synthesis of brevenal

Brevenal has received a significant amount of attention since its discovery due to its unique structure and its novle biological activity. Before discussing our efforts toward brevenal, a brief summary of the work from other groups is outlined here.

In 2006, Sasaki reported the first total synthesis of the initially proposed structure of brevenal.[34] They found that the ^{1}H NMR and ^{13}C NMR spectra for the synthetic material were not identical to those reported for the natural product. Later that year, they reported a revised synthesis where a detailed spectroscopic comparison suggested that the natural product was the C26 epimer of the originally proposed structure (Figure 1.8).[35]

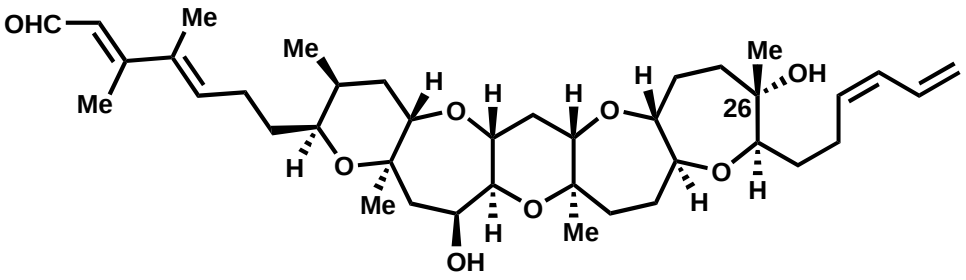
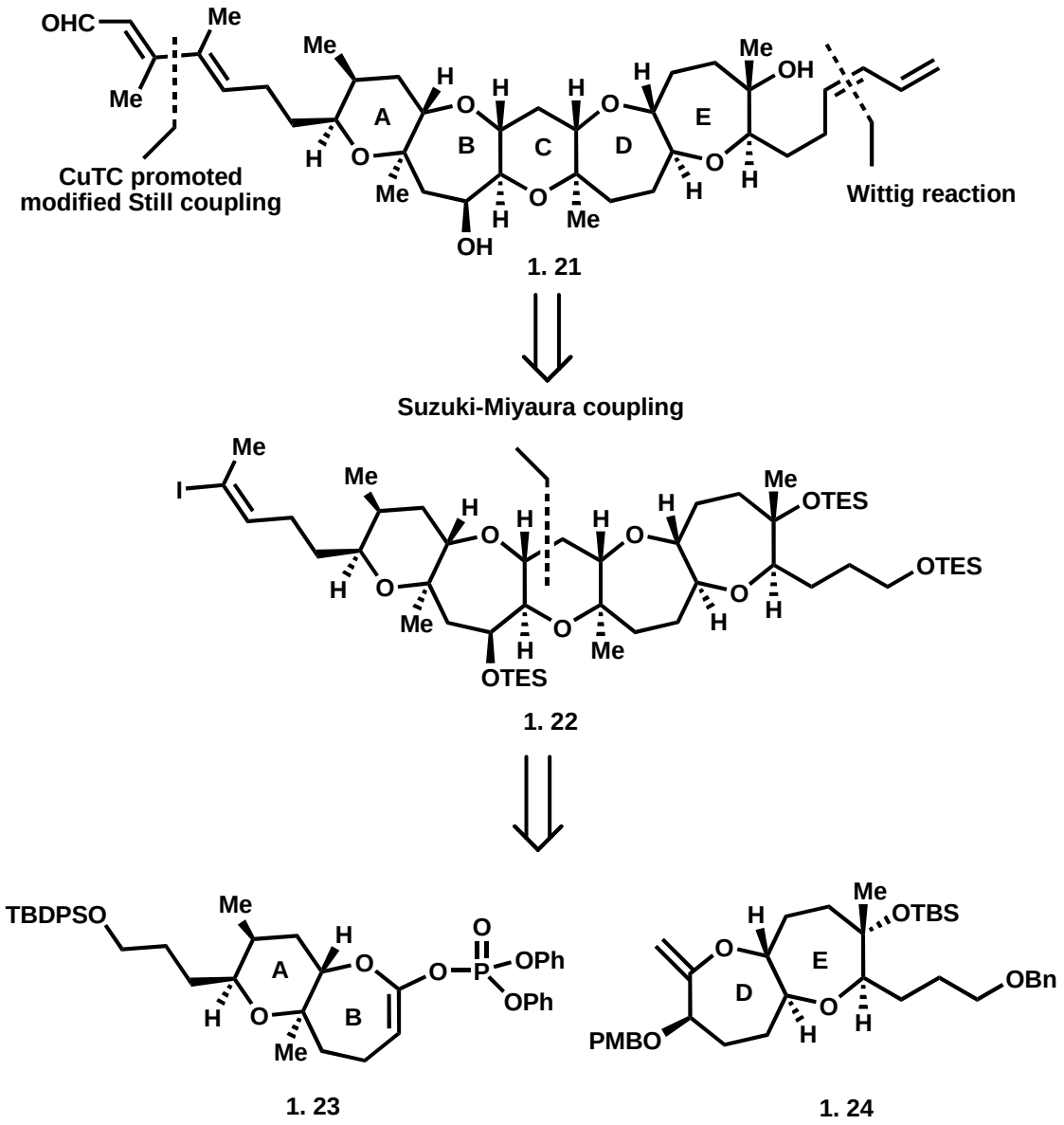


Figure 1.8. Revised structure of brevenal **1.21**

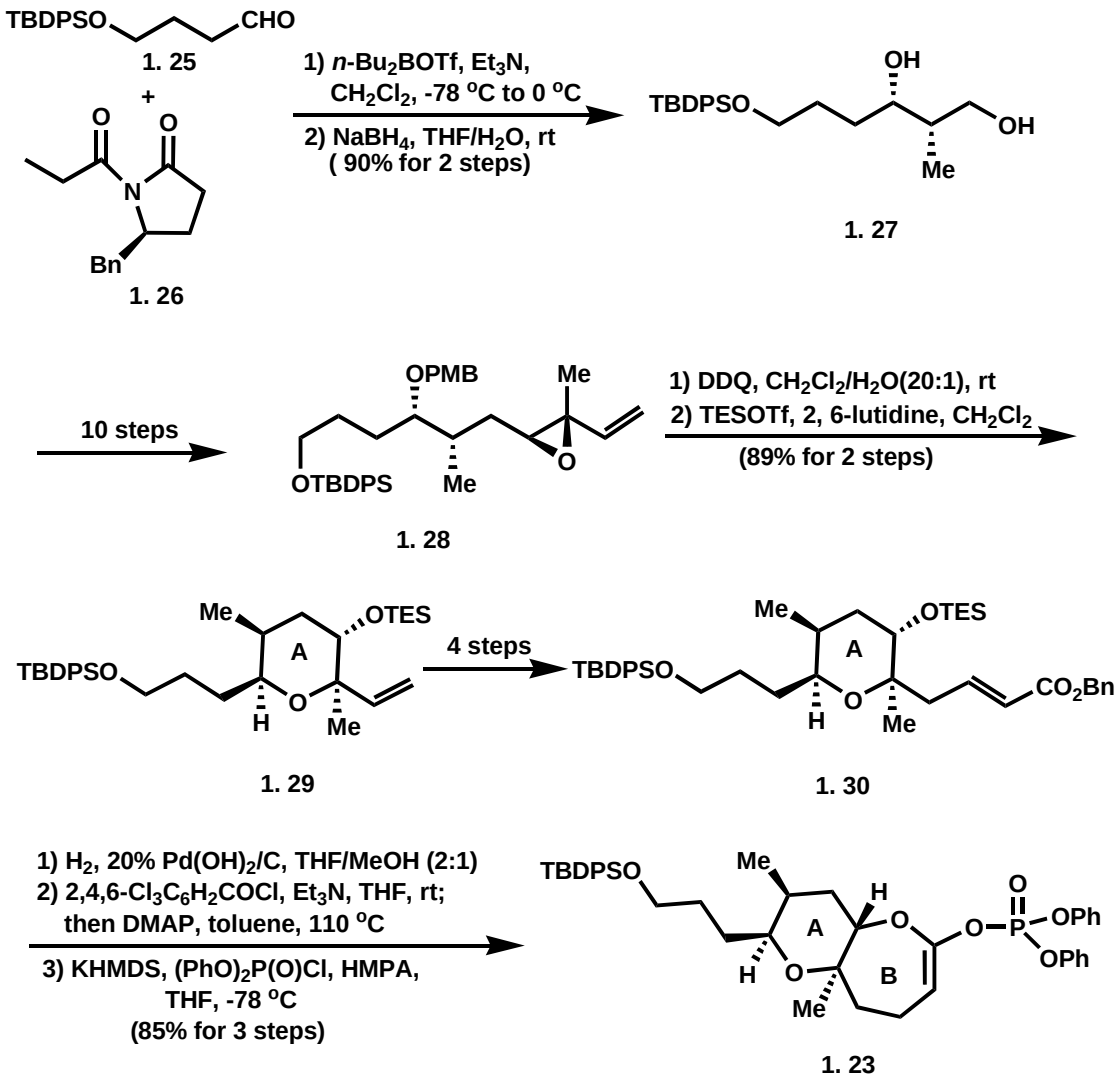
The key features of their synthesis included a convergent assembly of the pentacyclic polyether skeleton by a Suzuki-Miyaura coupling and a stereoselective construction of the left-hand (*E,E*)-diene system by a CuTC-promoted modified Stille coupling (Scheme 1.1).

The synthesis of AB ring fragment commenced with an Evans aldol reaction between aldehyde **1.25** and oxazolidinone **1.26**, which provided the *syn* aldol adduct (Scheme 1.2). The chiral auxiliary was reductively removed with $NaBH_4$ to provide 1,3-diol **1.27** as a single isomer. After 10 steps, epoxide **1.28** was formed. Deprotection of the PMB group followed by 6-endo cyclization afforded the A ring **1.29** after TES ether formation. Another four steps gave **1.30**. Hydrogenation of **1.30** with concomitant hydrogenolysis of the benzyl ester, followed by Yamaguchi lactonization generated a seven-membered lactone which was converted to AB ring enol phosphate **1.23** in 85% yield for three steps.

For the synthesis of DE ring fragment **1.24**, the known ether **1.31**[36] was chosen as a starting material (Scheme 1.3). Ether **1.31** was converted to primary triflate **1.32** in five steps. Then triflate **1.32** was subjected to nucleophilic displacement with allylmagnesium bromide in the presence of CuBr to afford olefin **1.33**. Next, Wacker-Tsuji reaction of the



Scheme 1.1. Sasaki's retrosynthetic analysis of brevenal



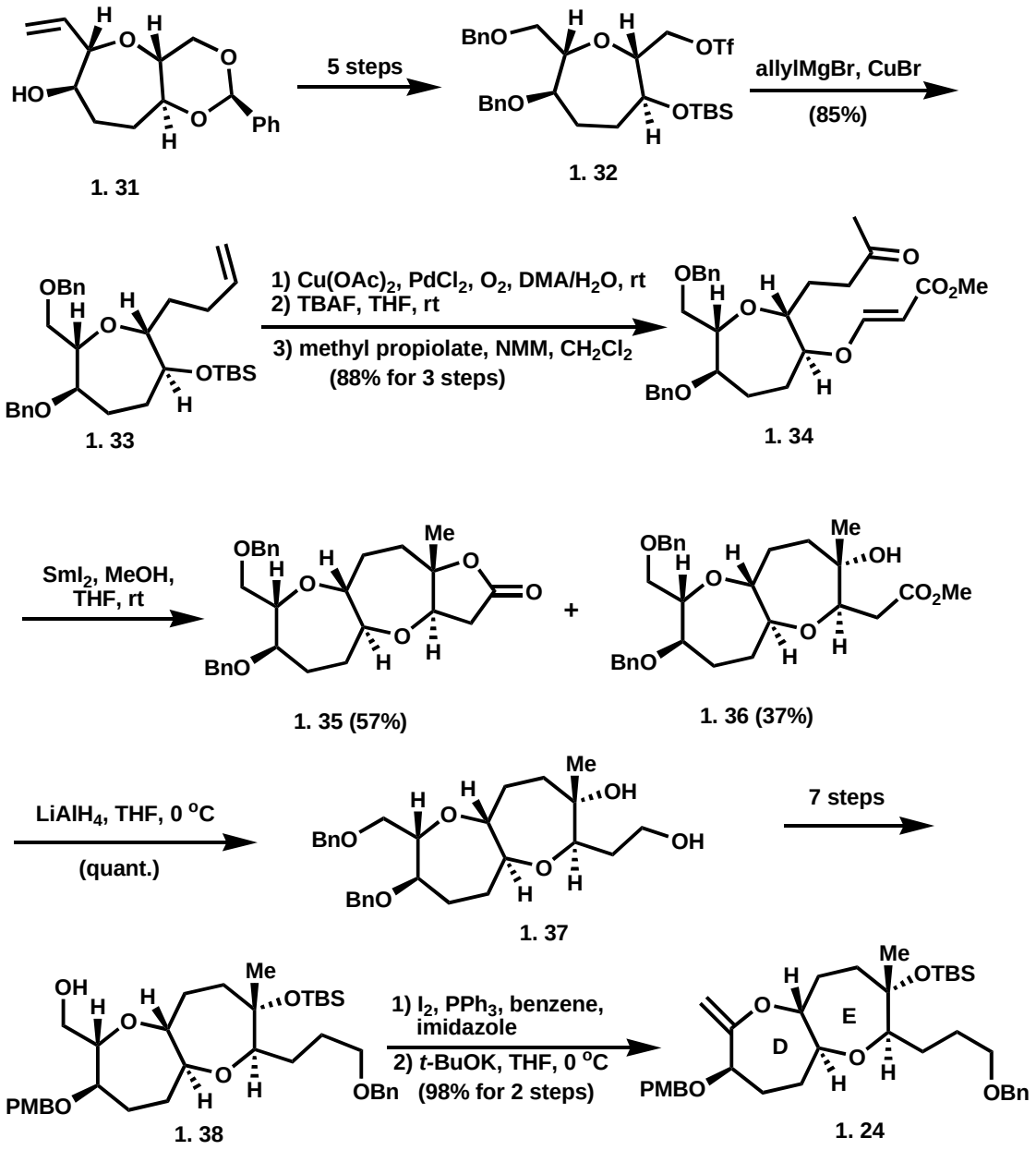
Scheme 1.2. Sasaki's synthesis of AB ring enol phosphate **1.23**

terminal olefin followed by deprotection and incorporation of a β-alkoxyacrylate provided **1.34** in 88% yield for three steps. Reductive cyclization of **1.34** with SmI_2 generated a mixture of **1.35** and **1.36** with the desired stereochemistry at C26. Each of these compounds was reduced to yield diol **1.37**. The subsequent seven steps included protecting group manipulation and one carbon elongation to generate **1.38**. Iodination and subsequent elimination afforded DE ring fragment **1.24** in 98% yield.

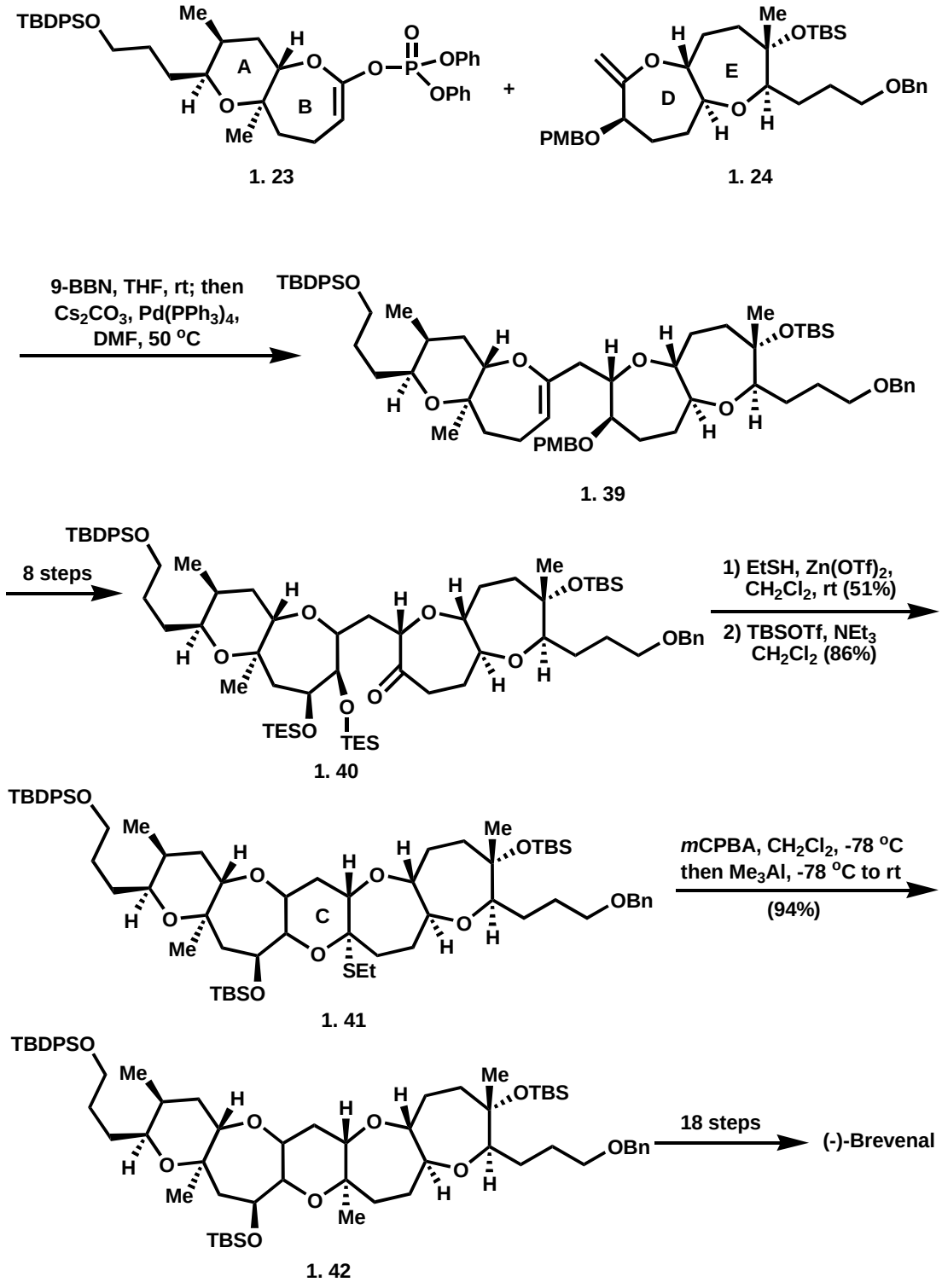
With the coupling fragments in hand, they assembled the pentacyclic polyether as shown in Scheme 1.4. Suzuki-Miyaura coupling between **1.23** and the alkylborane from **1.24** afforded **1.39**. Ketone **1.40** was formed in 8 steps involving hydroboration, oxidation, protection and Rubottom oxidation. In order to form the C ring, ketone **1.40** was treated with EtSH in the presence of $Zn(OTf)_2$ to generate thioacetal **1.41** after protection. Then thioacetal **1.41** was oxidized by *m*CPBA followed by addition of $AlMe_3$ to afford pentacyclic polyether **1.42** in good yield. The side chains were installed in 18 steps to finish (-)-brevenal. The longest linear sequence of Sasaki's synthesis was 68 steps. Sasaki's powerful coupling strategy led not only to the first total synthesis of brevenal but also to a revision of the proposed structure.

Yamamoto's total synthesis of brevenal

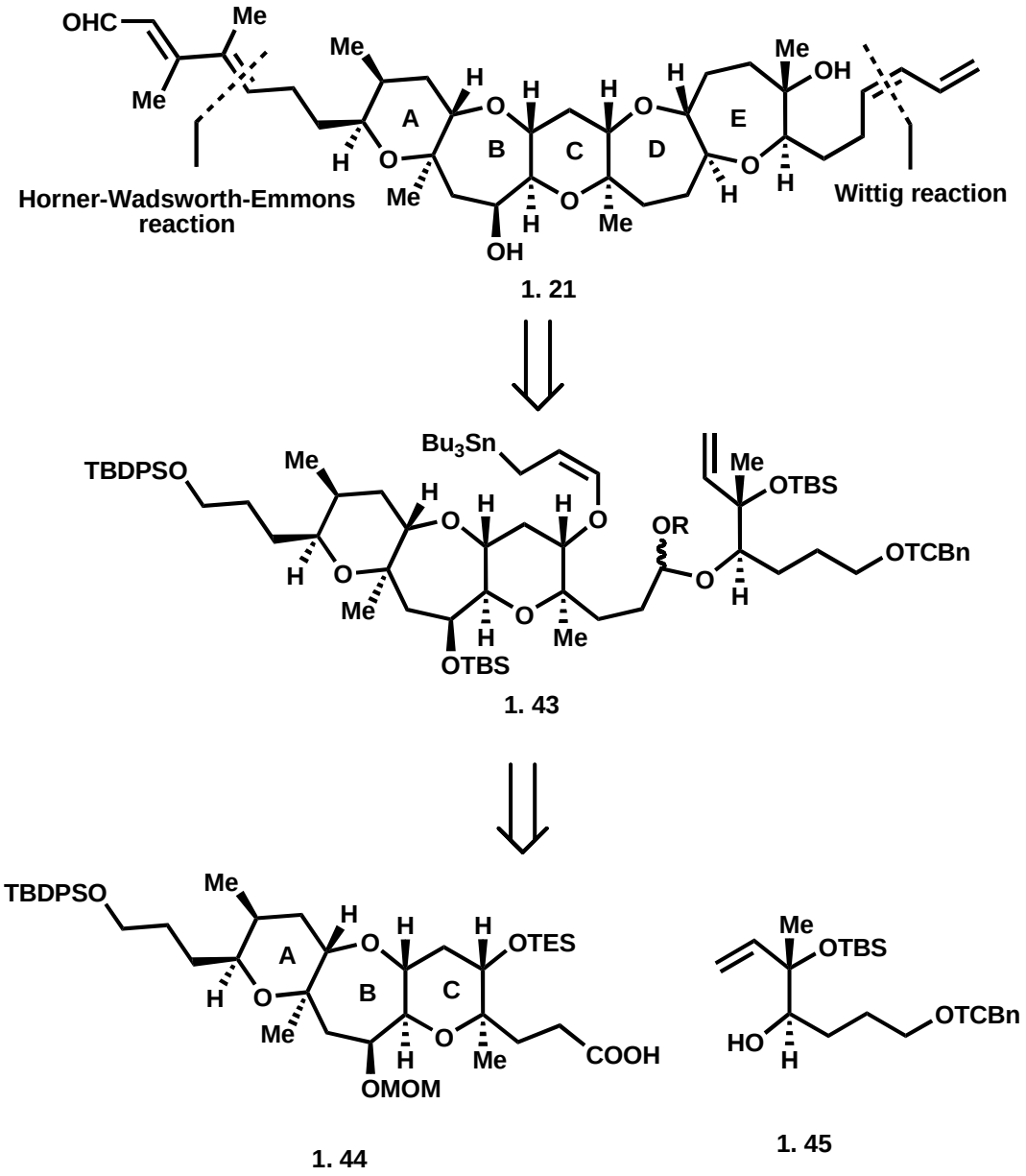
In 2009, Kadota and Yamamoto published their total synthesis of brevenal.[37] They used a Horner-Wadsworth-Emmons reaction to install the left-hand side chain and a Wittig reaction to install the right-hand side chain. The pentacyclic ether core was constructed by an intramolecular allylation of an α-acetoxy ether and a subsequent ring-closing metathesis (Scheme 1.5).



Scheme 1.3. Sasaki's synthesis of DE ring exocyclic enol ether **1.24**



Scheme 1.4. Sasaki's synthesis of the pentacyclic polyether core



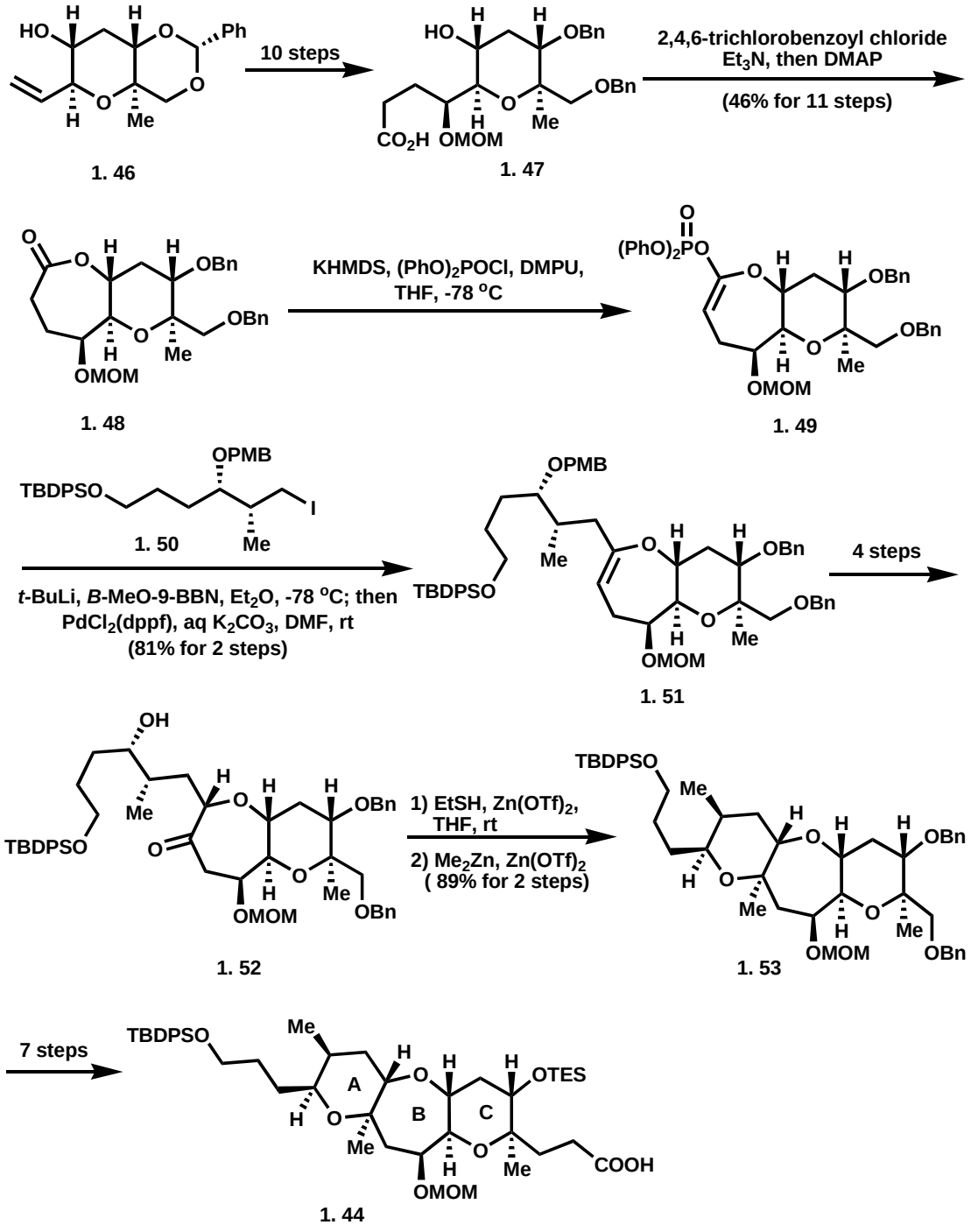
Scheme 1.5. Yamamoto's retrosynthetic analysis of brevenal

The synthesis of the ABC ring fragment **1.44** is outlined in Scheme 1.6. The known compound **1.46**[38] was converted to key intermediate **1.47** in 10 steps. Yamaguchi lactonization set the 6,7 fused ring system. Enol phosphate **1.49** was formed under the usual conditions. Then a Suzuki-Miyaura coupling of **1.49** and the alkyl borate from **1.50** afforded enol ether **1.51**. After 4 steps, **1.51** was converted to ketone **1.52**. Cyclization took place using EtSH/$Zn(OTf)_2$ to generate the thioacetal which was subjected to Me_2Zn, $Zn(OTf)_2$ to install the angular methyl group in 89% yield. The intermediate **1.53** was converted to the coupling partner **1.44** in additional 7 steps.

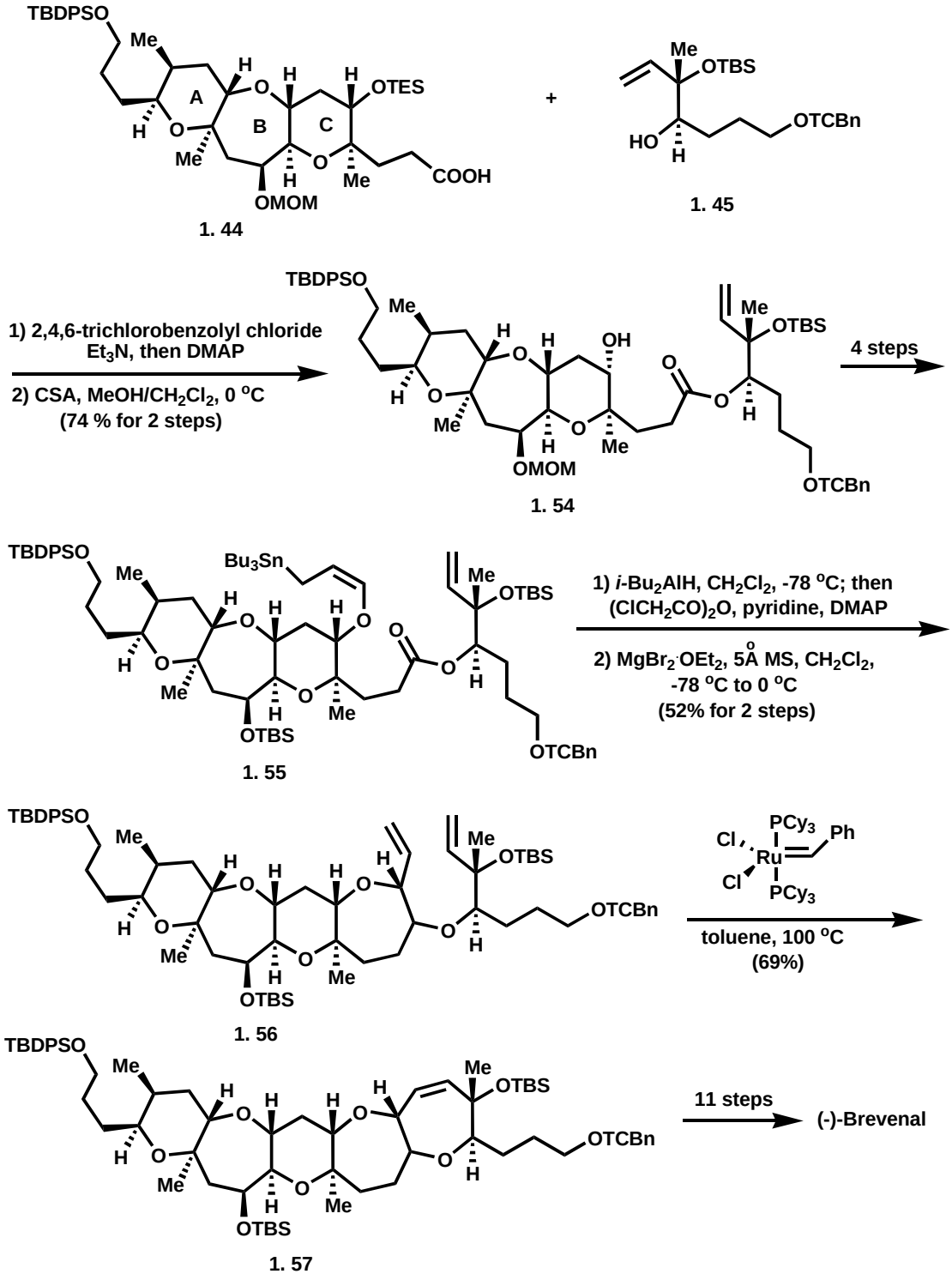
Scheme 1.7 describes the synthesis of the pentacyclic polyether core. A Yamaguchi esterification between the two key segments generated ester **1.54** after TES deprotection using camphorsulfonic acid. After additional 4 steps, stannane **1.55** was formed. Modified Rychnovsky acetylation of ester **1.55** provided the α-chloroacetoxy ether which underwent intramolecular allylation by $MgBr_2 \cdot OEt_2$ to give **1.56**. Ring-closing metathesis of diene **1.56** led to pentacyclic ether **1.57** in 69% yield. After another 11 steps, brevenal was formed. The longest linear sequence in Yamamoto's synthesis was 57 steps with a 0.84% overall yield.

Crimmins' approach towards brevenal

In 2010, Crimmins reported their progress towards brevenal.[39] A Horner-Wadsworth-Emmons olefination was planned to couple the AB-ring and E-ring (Scheme 1.8). Construction of the AB-ring and E-ring fragments would be achieved through an asymmetric alkylation/ring-closing metathesis strategy.



Scheme 1.6. Yamamoto's synthesis of ABC ring acid **1.44**

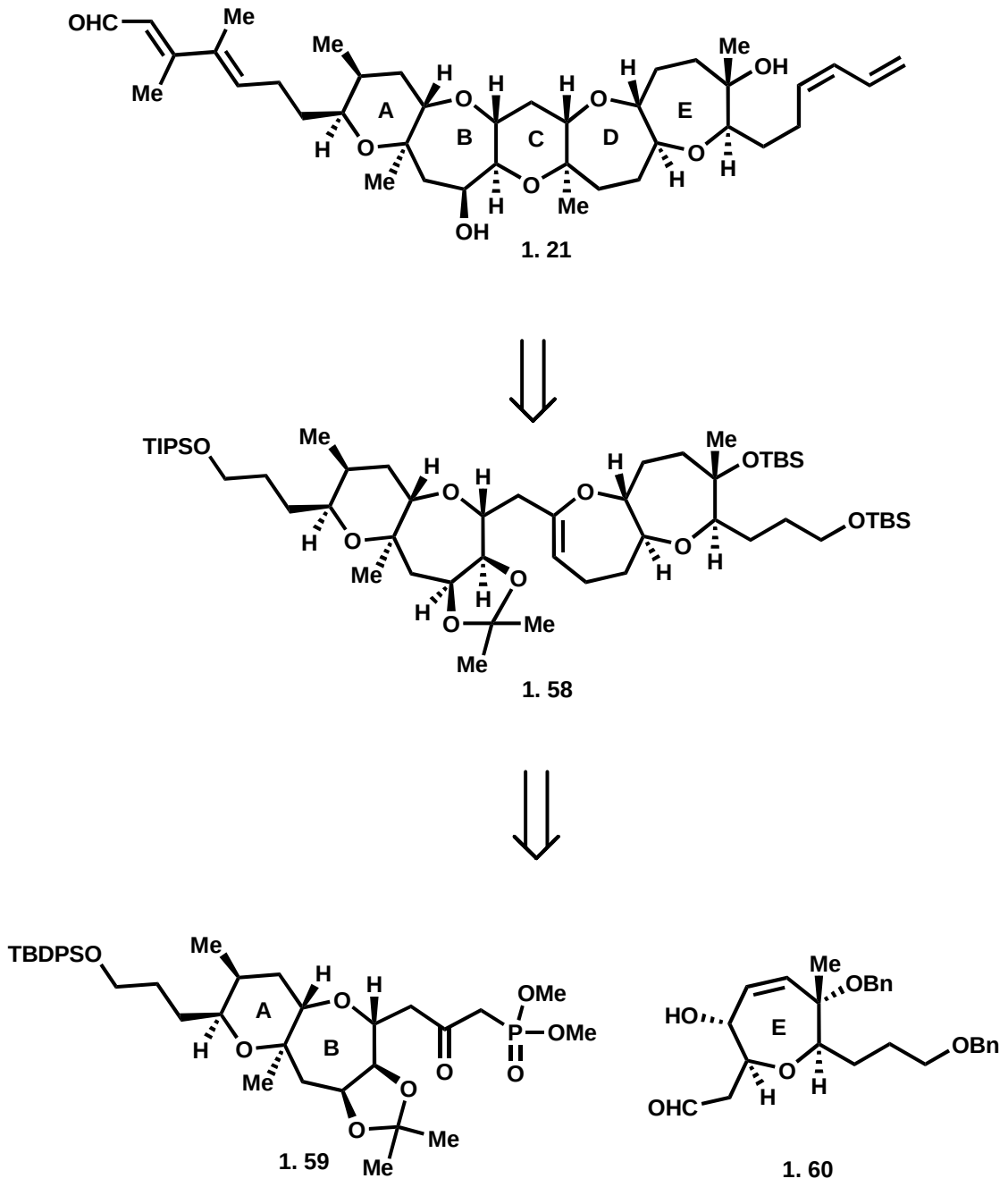


Scheme 1.7. Yamamoto's synthesis of the pentacyclic polyether core

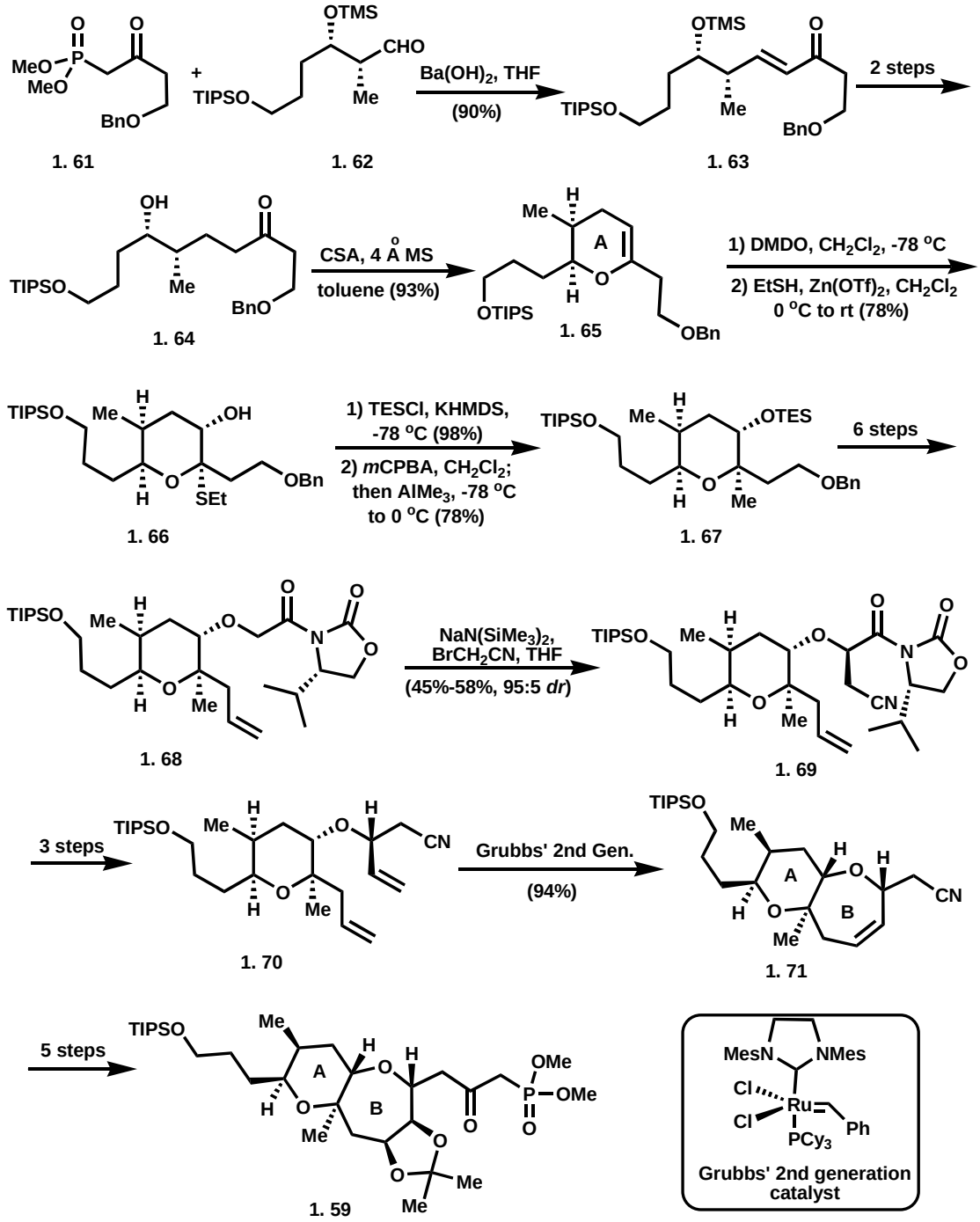
The synthesis of the AB-ring subunit started with a Horner-Wadsworth-Emmons olefination between **1.61** and **1.62** (Scheme 1.9). After further transformations, **1.64** was cyclized under acidic condition to give enol ether **1.65**. The angular methyl group was installed in three steps: 1) thioacetal **1.66** formation via an epoxide intermediate, 2) protection of the hydroxyl group as a TES ether and 3) methyl group installation by *m*CPBA /$AlMe_3$. After six steps, **1.67** was converted into oxazolidinone **1.68**. Treatment of the sodium enolate of **1.68** with bromoacetonitrile resulted in a highly diastereoselective glycolate alkylation to furnish the nitrile **1.69**. In another three steps, **1.69** was converted to diene **1.70**. Ring-closing metathesis by Grubbs' second generation catalyst afforded **1.71**. Then **1.71** was converted to *β*-ketophosphonate **1.59** in five steps.

The synthesis of the E-ring began with an asymmetric aldol addition between oxazolidinone **1.72** and aldehyde **1.73** (Scheme 1.10). The product **1.74** was converted to aldehyde **1.75** in four steps. A Wittig reaction followed by deprotection gave homoallylic alcohol **1.76**. Alkylation of **1.76** with bromoacetic acid followed by coupling with valine-derived oxazolidinone **1.77** generated **1.78**. Then, diastereoselective alkylation of **1.78** with bromoacetonitrile gave **1.79** which was converted to diene **1.80** as a diastereomeric mixture in three steps. Treatment of diene **1.80** with Grubbs' second generation catalyst led to the formation of **1.81** in 91% yield. After four steps, aldehyde **1.60** was formed.

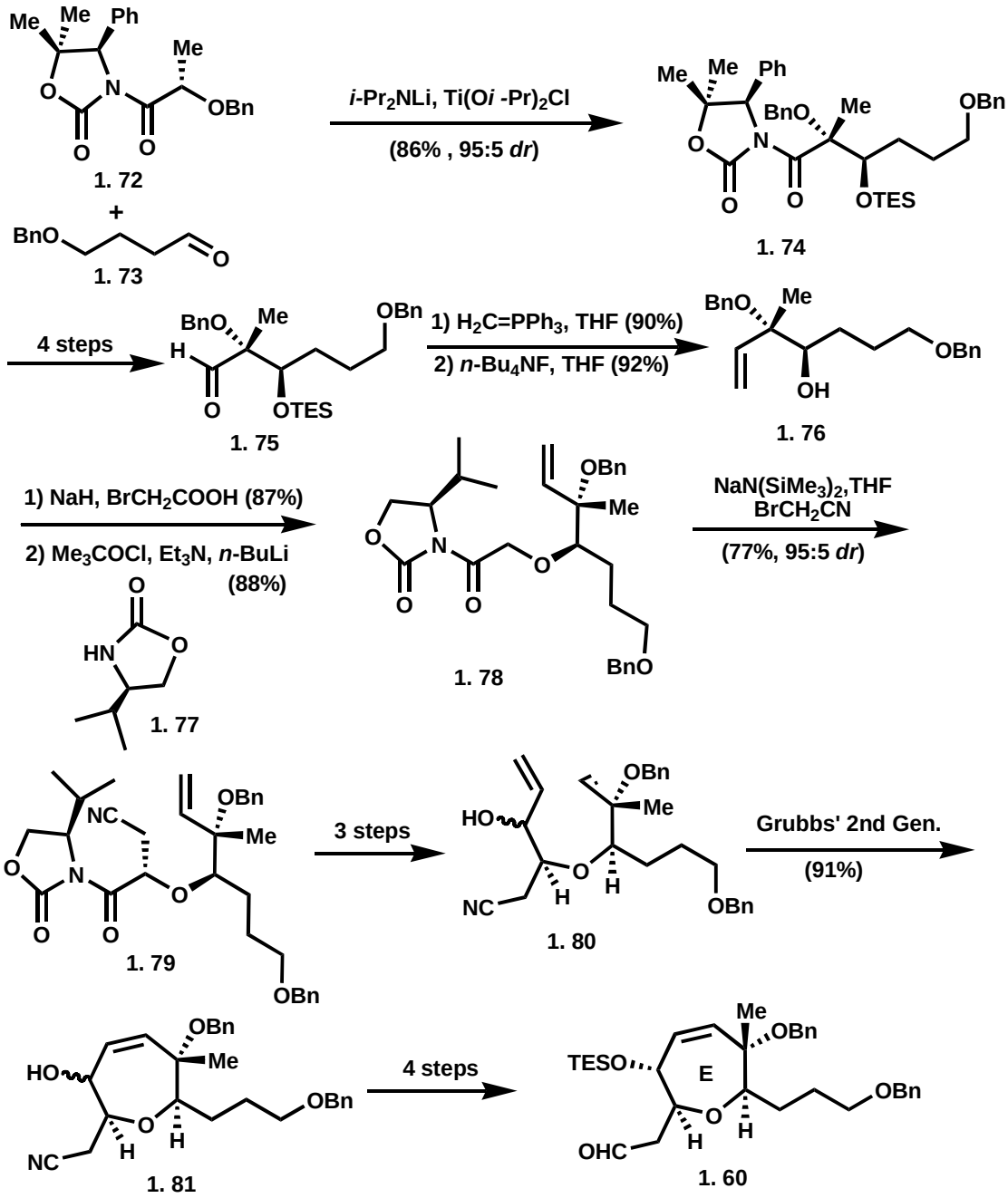
With both coupling partners in hand, they pushed one step further. The Horner-Wadsworth-Emmons reaction between *β*-ketophosphonate **1.59** and aldehyde **1.60** afforded enone **1.82** in 90% yield (Scheme 1.11). So far, they proved the coupling stragety is efficient to enable them to finish the total synthesis of brevenal.



Scheme 1.8. Crimmins' retrosynthetic analysis of brevenal



Scheme 1.9. Crimmins' synthesis of AB ring subunit



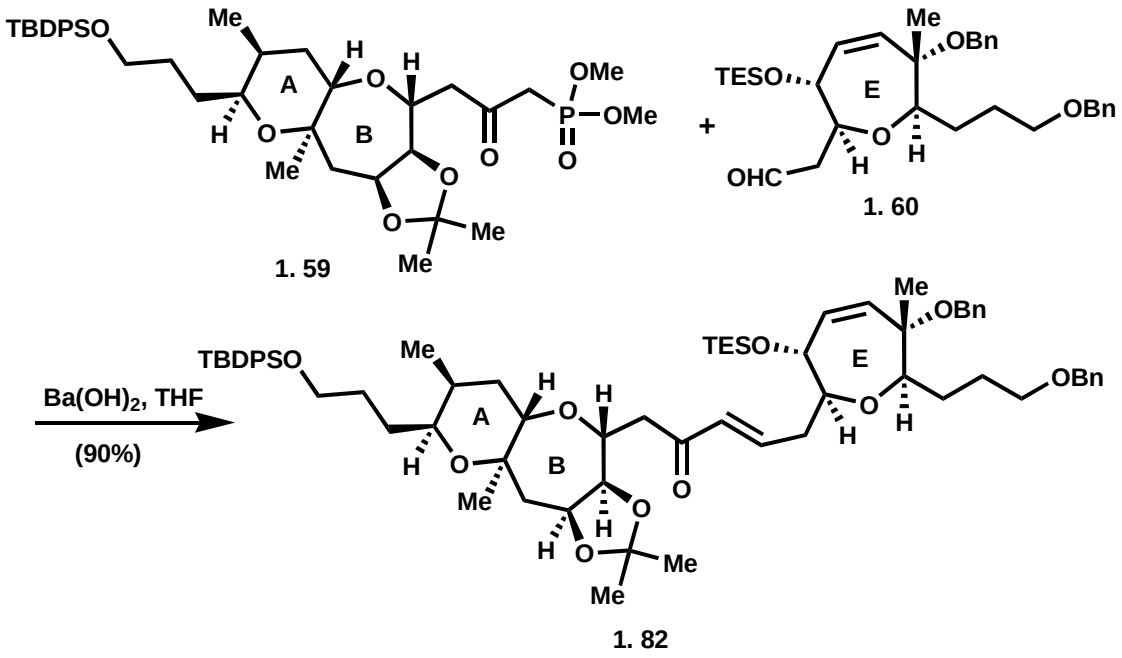
Scheme 1.10. Crimmins' synthesis of E-ring subunit **1.60**

Results and Discussion

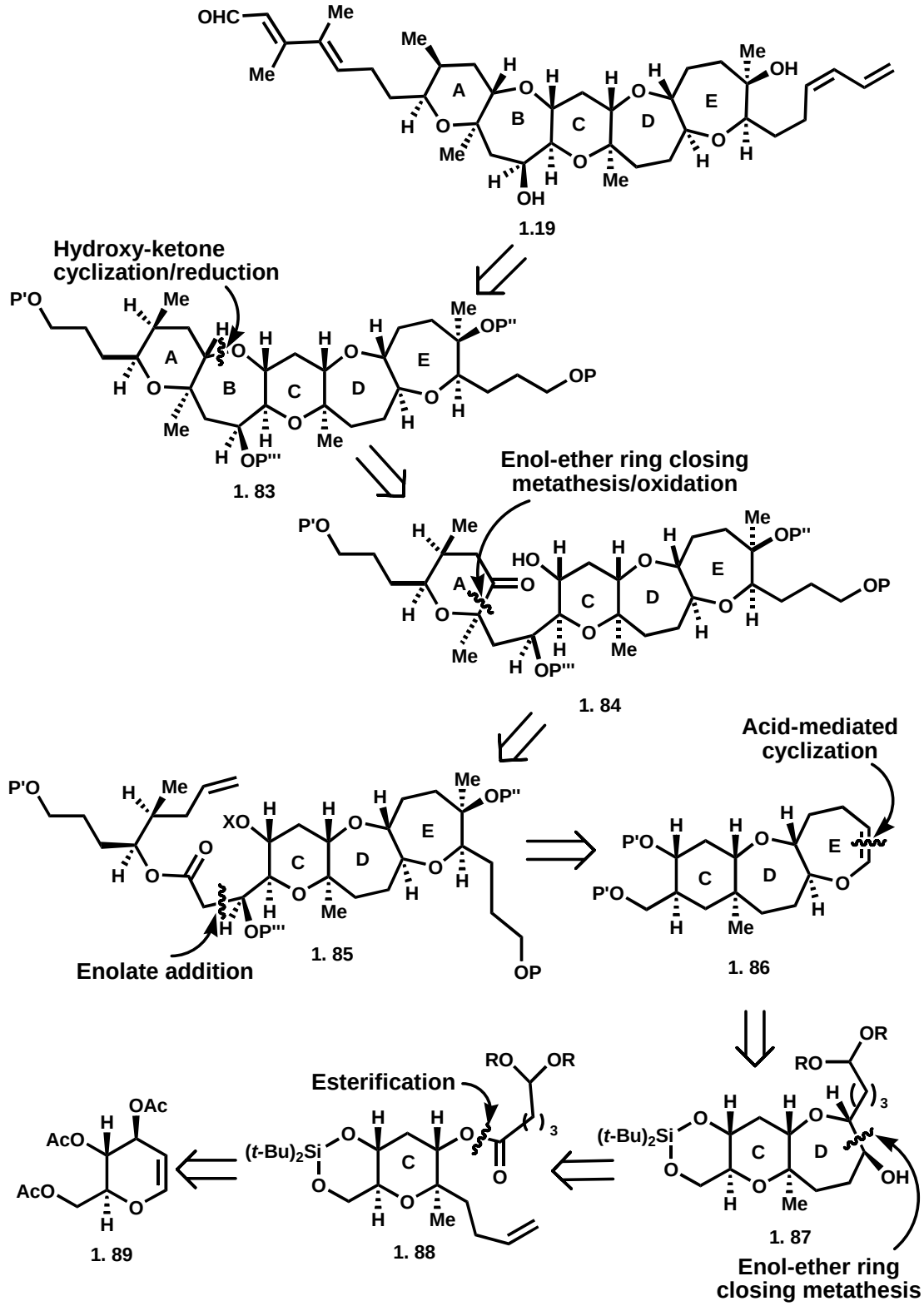
First generation of brevenal

The intriguing structure and unique biological activities of the marine ladder toxins have also attracted our attention. In addition to the interest in ion channel binding properties, our successful experiences with hemibrevetoxin B,[40] gambierol[41] and gambieric acid A[42] encouraged us to pursue the synthesis of brevenal.

The retrosynthetic plan is outlined in Scheme 1.12. At that time, Sasaki and co-workers had not published their total synthesis of brevenal. So we began our work targeting the initially proposed brevenal. The side chains would be incorporated at the end of the synthesis. The B-ring would come from a hydroxy-ketone cyclization and reduction sequence. The A-ring would come from an enol-ether RCM (ring closing



Scheme 1.11. Crimmins' coupling between AB-ring subunit and E-ring subunit

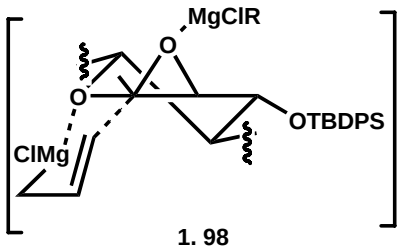


Scheme 1.12. Retrosynthetic analysis of brevenal **3.19**

metathesis) reaction sequence. The fully functionalized C-E ring system **1.85** would be synthesized by a Mukaiyama aldol reaction. The E-ring would be in turn come from an acid mediated cyclization and the D-ring would be constructed using a Takai/ring closing metathesis sequence. The fully functionalized C-ring **1.88** would come from tri-*O*-acetyl-L-glucal. Our work began with the lower cost D-glucal derivative that would lead to the enantiomer of the natural product.

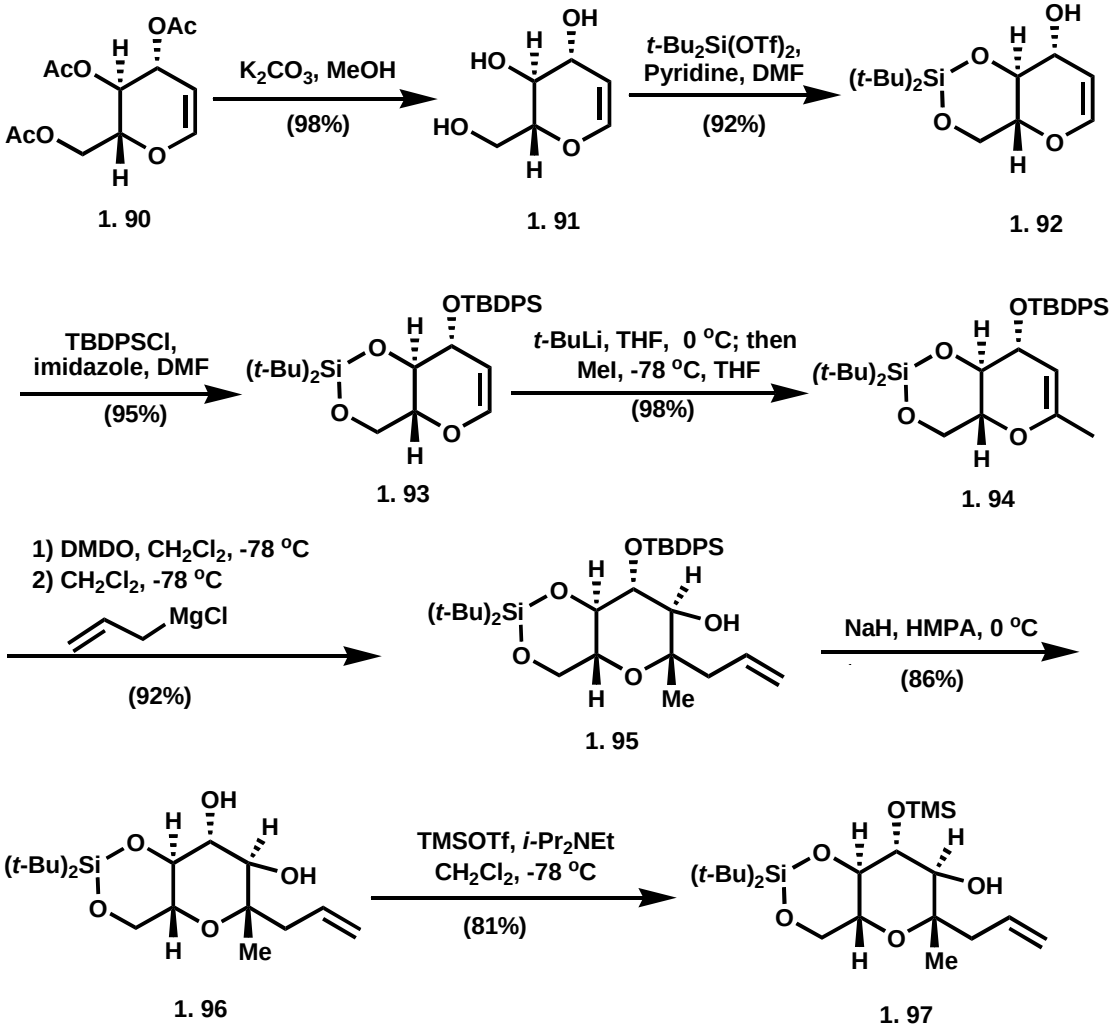
Hydrolysis of tri-*O*-acetyl-D-glucal **1.90** afforded D-glucal **1.91** in 98% yield. The hydroxyl groups at the C-4 and C-6 positions were simultaneously protected as the silyl ethers. The C-3 hydroxyl group was protected as a TBDPS ether to afford **1.93**. Then cyclic enol ether **1.93** was methylated at the α-C to give compound **1.94** in 98% yield. Oxidation of **1.94** with DMDO and addition of allylmagnesium chloride to the intermediate epoxide gave secondary alcohol **1.95** as a single diastereomer in 92% yield. The stereochemical outcome of this reaction could be explained by coordination of the Mg counterion to the axial lone pair of the pyranyl oxygen and ligand transfer via six membered transition structure **1.98**[43] (Figure 1.9). Selective removal of the TBDPS group by NaH afforded diol **1.96** in 86% yield. After selective protection, we arrived at TMS ether **1.97** (Scheme 1.13).

5,5-dimethoxypentanoic acid which would react with alcohol **1.97** was prepared according to the procedure[44] shown in Scheme 1.14. Methanolysis of δ-valerolactone gave hydroxy-ester **1.100** after refluxing for 3 days. Oxidation of the free alcohol afforded aldehyde **1.101** which was protected as the corresponding dimethyl acetal to give **1.102** in 50% yield for the three steps. Hydrolysis of ester **1.102** afforded acid **1.103** in 92% yield.



1. 98

Figure 1.9. Explanation for the stereochemical outcome



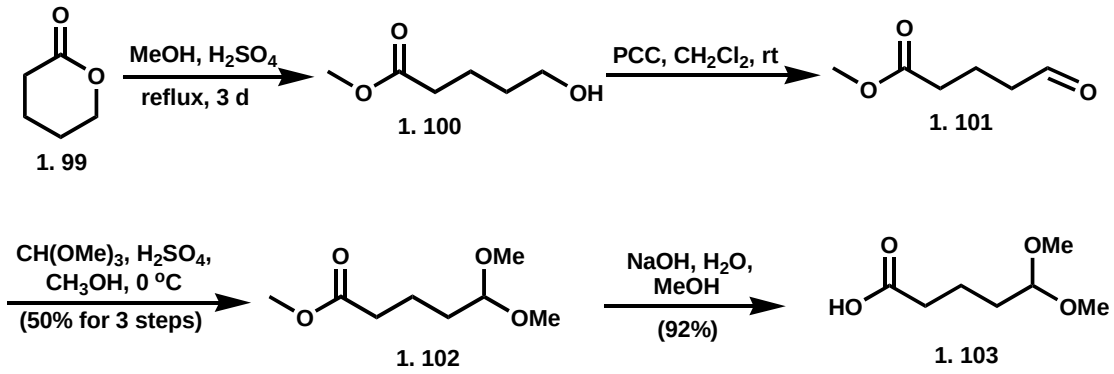
1. 90 1. 91 1. 92

1. 93 1. 94

1. 95

1. 96 1. 97

Scheme 1.13. Synthesis of the C-ring derivative

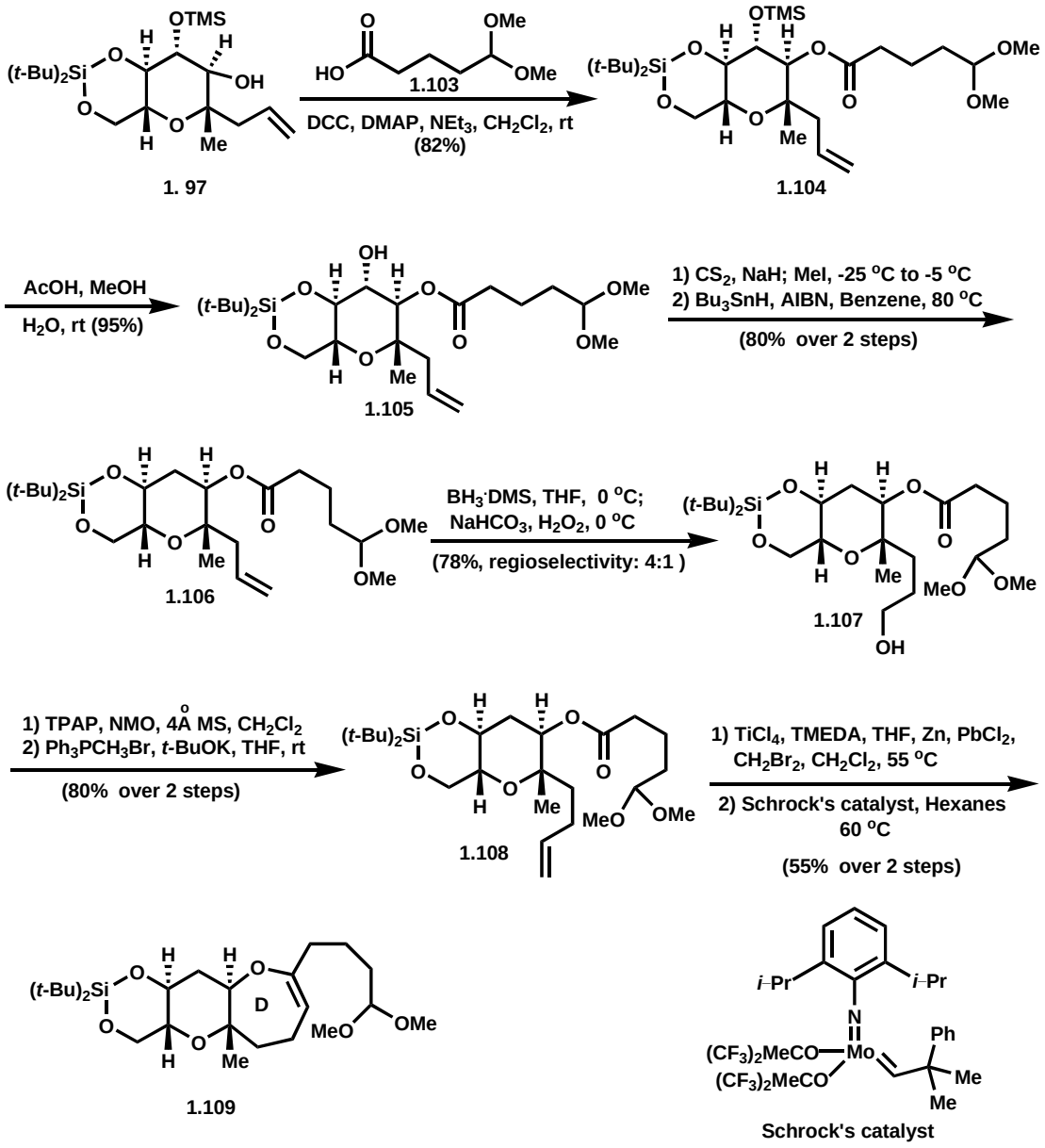


Scheme 1.14. Synthesis of 5,5-dimethoxypentanoic acid **1.103**

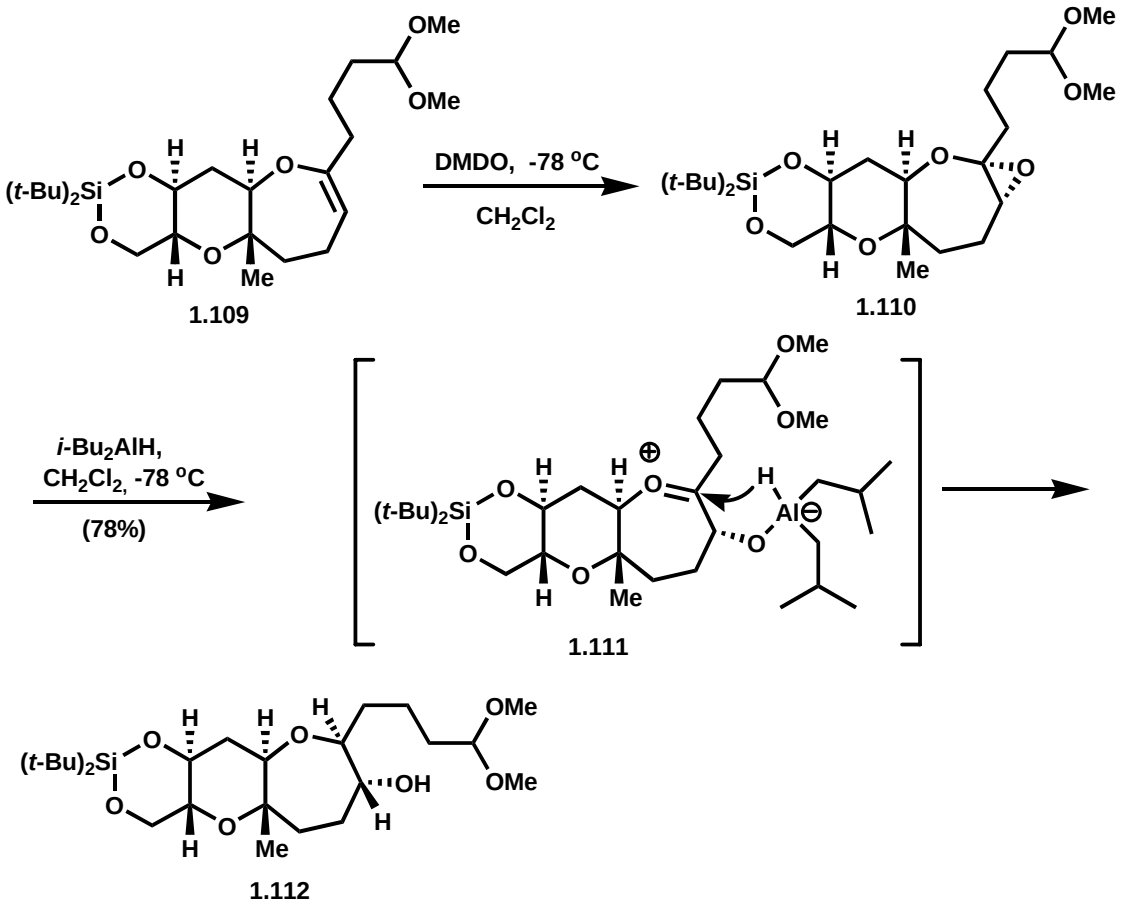
Steglich esterification between **1.97** and **1.103** generated ester **1.104** in 82% yield (Scheme 1.15). Removal of the TMS group gave **1.105** in 95% yield. Barton deoxygenation afforded compound **1.106** in 80% yield over two steps. One-carbon homologation of allyl derivative **1.106** began with a hydroboration/oxidation reaction to give primary alcohol **1.107**. Oxidation to the aldehyde using TPAP/NMO and Wittig methylenation gave homoallyl derivative **1.108**. At this stage, olefinic-ester **1.108** was converted into the corresponding acyclic enol ether which was then cyclized using Schrock's molybdenum catalyst to afford seven-membered enol ether **1.109** in 55% yield over the two steps**.** However, Grubbs 2nd generation catalyst afforded only a 30% yield of **1.109**.

The tricycle **1.109** was oxidized with DMDO to give an epoxide that was reduced by *i*Bu_2AlH to give secondary alcohol **1.112** in 78% yield as a single diastereomer (Scheme 1.16). This result was consistent with the DFT calculation on the DMDO epoxidation of a related substrate.[45] We believe that torsional interactions between the *pseudo*-axial allylic proton and DMDO in the transition state result in epoxidation from the lower face as indicated in Figure 1.10. After **1.110** was formed, reduction by *i*Bu_2AlH afforded product **1.112** presumable via an intramolecular hydride transfer as indicated in **1.111**.

The E-ring in **1.113** was generated using a hydroxy-acetal cyclization and elimination using PPTS and pyridine. Enol ether **1.113** was oxidized by DMDO to afford a mixture of the corresponding epoxides which were allowed to react with allylmagnesium chloride to give secondary alcohols **1.114** and **1.115** as a 2:1 mixture (78% yield) favoring the desired product **1.114** (Scheme 1.17).



Scheme 1.15. Formation of the D-ring



Scheme 1.16. Oxidation of the D-ring

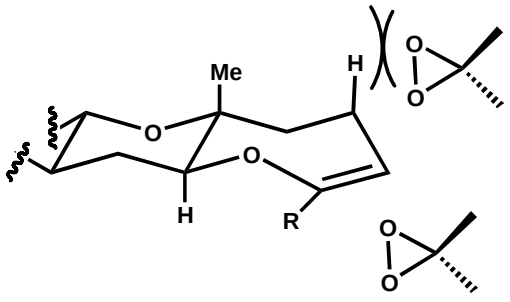
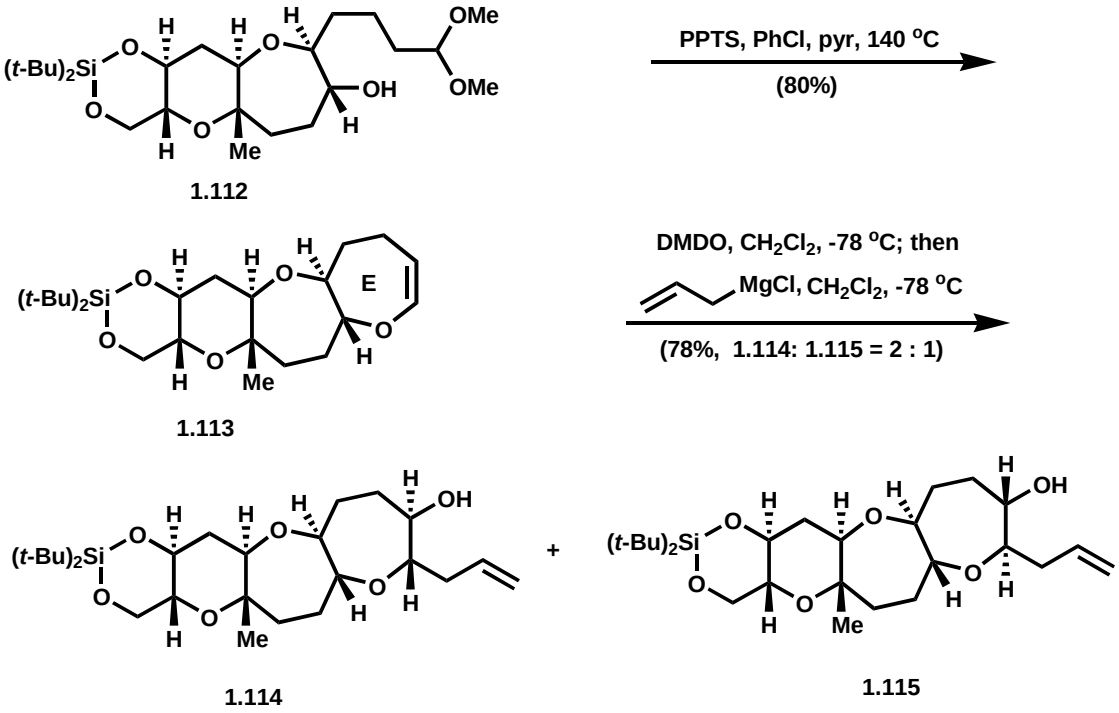


Figure 1.10. Rationale for D-ring oxidation

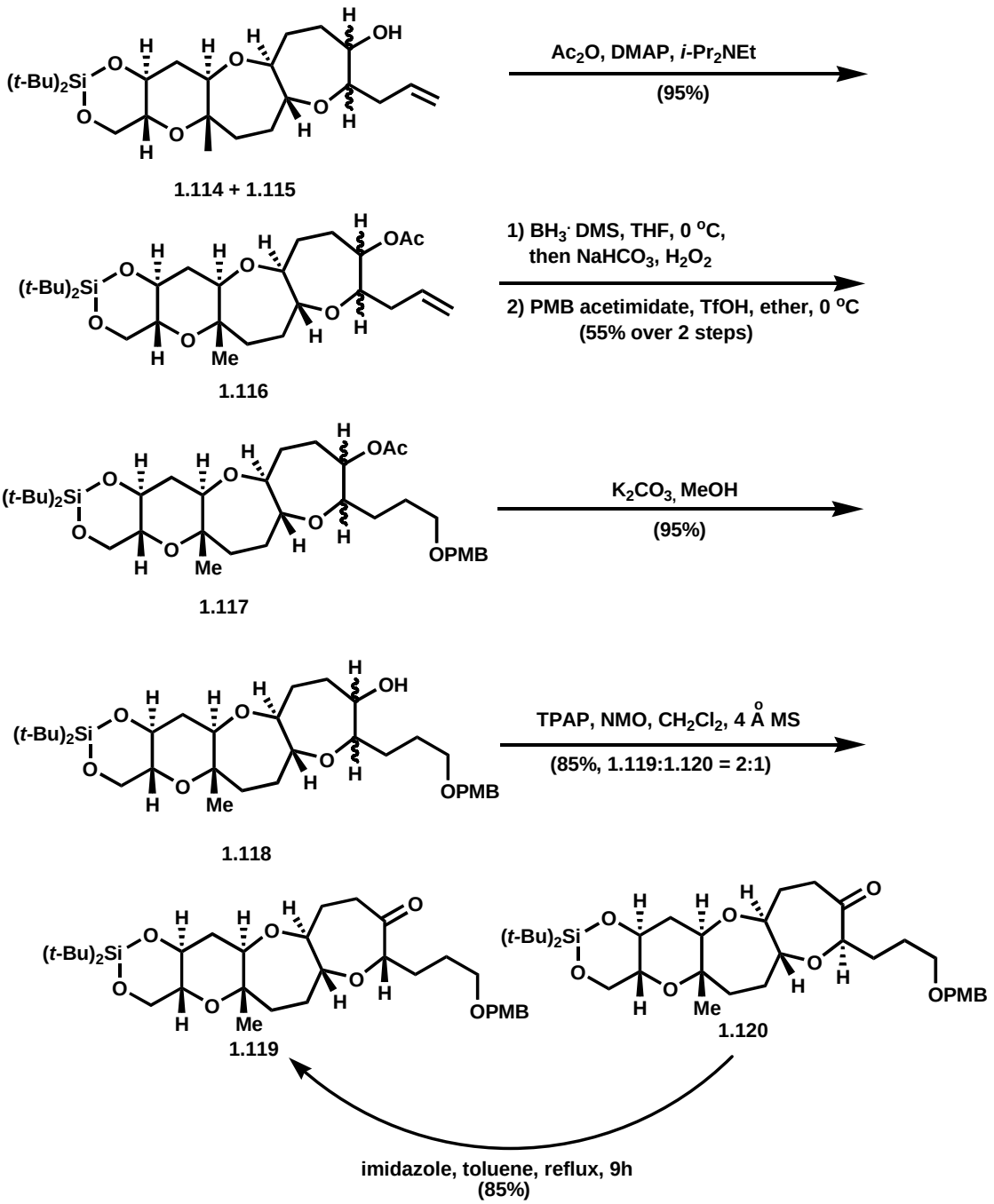


Scheme 1.17. Synthesis of the E-ring

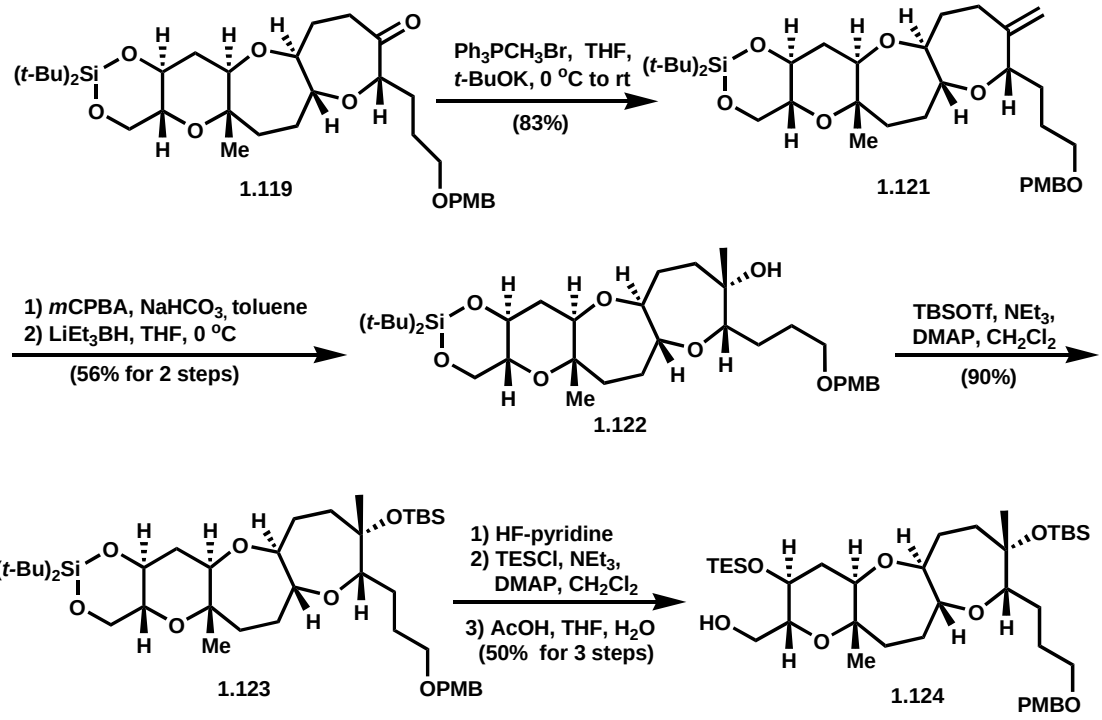
The mixture of **1.114** and **1.115** was acylated and the olefins were subjected to a hydroboration/oxidation to give **1.117** after PMB ether formation. The acetate was removed using potassium carbonate. Oxidation of the alcohol **1.118** using TPAP/NMO gave a mixture of ketones in 85% yield. At this stage, the two isomers **1.119** and **1.120** were separated and the minor isomer **1.120** was equilibrated using imidazole to provide the desired product **1.119** in 85% yield (Scheme 1.18).

The completion of our first generation synthesis of the C-E ring system is given in Scheme 1.19. During our initial studies, the stereochemistry for the tertiary alcohol had not been revised by Sasaki. Thus, we performed a three-step sequence to install the axial alcohol. Ketone **1.119** was subjected to a Wittig reaction to form 1,1-disubstituted olefin **1.121** in 83% yield. Olefin **1.121** was epoxidized by *m*CPBA and then reduced by $LiEt_3BH$ to provide desired tertiary alcohol **1.122** that corresponded to the proposed structure of brevenal in 56% yield over two steps. The relative stereochemistry of **1.122** was confirmed by nOe experiments. **1.122** was protected as a TBS ether to give **1.123** in 90% yield**.** The silylene in **1.123** was selectively removed with HF·pyridine to give the corresponding diol that was diprotected as the corresponding TES ethers. The primary alcohol was released using AcOH to afford **1.124** in 50% yield over the three steps.

As we were completing our work to the C-E ring system, Sasaki and co-workers published their brevenal total synthesis. It became clear to that our synthesis of the C-E ring subunit was too long to enable us to efficiently complete the synthesis and to generate analogs. Thus as outlined below, we set out on a new approach to brevenal.



Scheme 1.18. Synthesis of the E-ring derivative

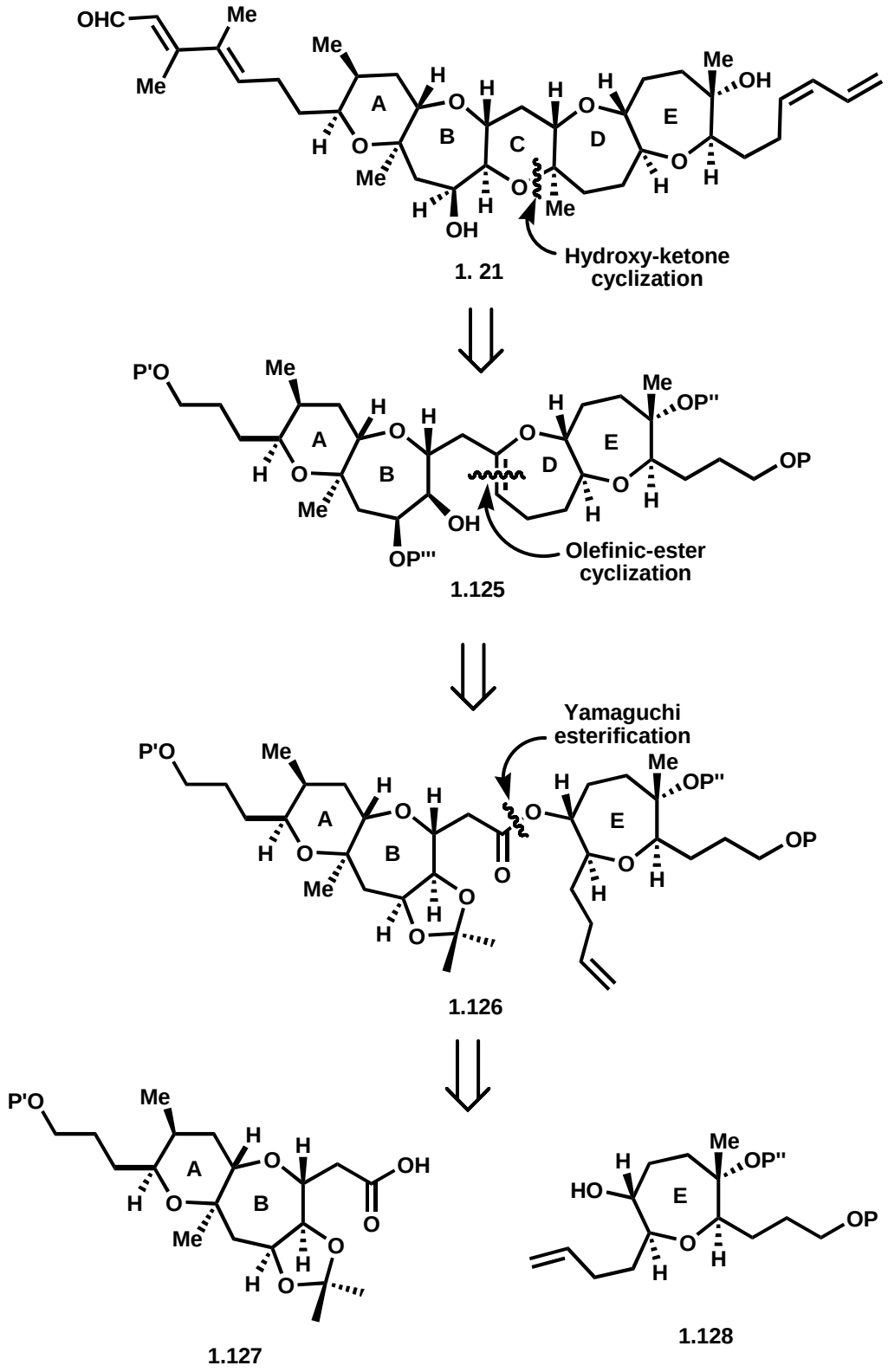


Scheme 1.19. Completion of the fully functionalized C-E ring

Second generation of brevenal

Our second generation retrosynthetic plan is outlined in Scheme 1.20. As in our initial approach, the side chains would be incorporated at the end of the synthesis. The C-ring would come from a hydroxy-ketone cyclization and reduction sequence. The D-ring would come from olefinic-ester cyclization. Intermediate **1.126** would come from an esterification between the AB-ring moiety **1.127** and the E-ring **1.128**. In addition to enabling us to more efficiently generate brevenal and analogs, this approach would result in the synthesis of the correct enantiomer of brevenal.

The synthesis of the E-ring subunit began with (L)-glyceraldehyde acetonide **1.129**.[46] Addition of homoallylmagnesium bromide (prepared from 4-bromo-1-butene) to aldehyde **1.129**, in the presence of $ZnCl_2$ afforded alcohol **1.130** as the major isomer.

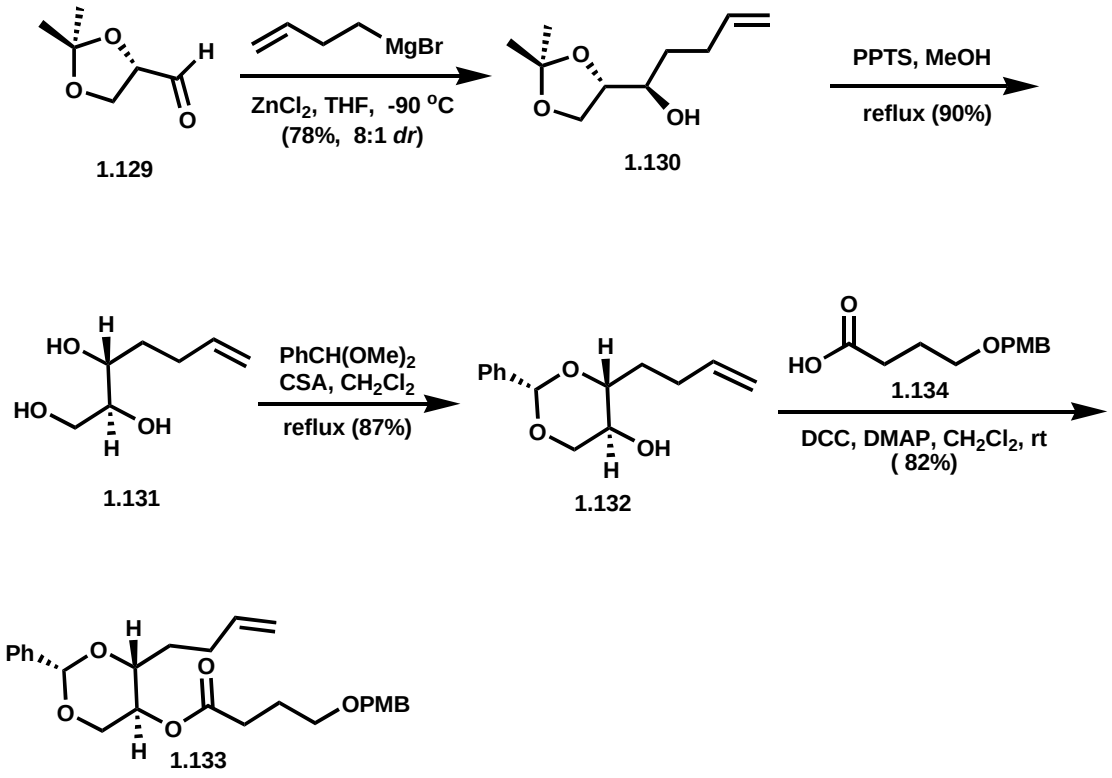


Scheme 1.20. Retrosynthetic analysis of brevenal

Acetonide **1.130** was deprotected using PPTS, MeOH to give triol **1.131** in 90% yield. Triol **1.131** was selectively protected as the corresponding benzylidene to give **1.132** in 87% yield (Scheme 1.21). It is worthwhile to mention that refluxing conditions decreased the amount of five-membered ring (benzylidene acetal of 1,2-diols) formation from 30% to less than 10%. Steglich esterification between **1.132** and 4-(4-methoxybenzyloxy) butanoic acid **(**prepared according to a known procedure[47] as shown in Scheme 1.22) provided olefinic-ester **1.133** in 82% yield.

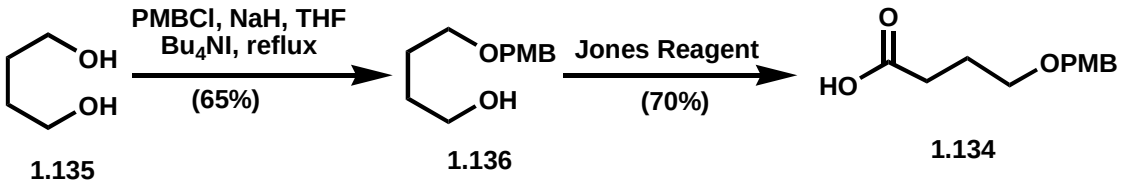
With olefinic-ester **1.133** in hand, we were prepared to test the cyclization chemistry (Scheme 1.23). A general method of making cyclic enol ethers is a two-step protocol: 1) ester to acyclic enol ether formation (Takai reaction) 2) ring closing metathesis. By using a titanium methylidene reagent, the Takai reaction provided the acylic enol exclusively. Ring closing metathesis using the Grubbs' second generation catalyst gave a 35%-40% yield of cyclic enol ether **1.138** together with a significant amount of byproducts coming from isomerization of the olefin. In contrast, the use of the titanium ethylidene reagent on ester **1.134** gave cyclic enol ether **1.138** in 68% yield together with 22% of acyclic enol ether **1.139** which could be converted into **1.138** in 20% yield using the Grubbs' second generation catalyst under an atmosphere of ethylene.

Cyclic enol ether **1.138** was oxidized by DMDO to give the corresponding epoxide. Reduction with *i*Bu_2AlH afforded secondary alcohol **1.140** as the major product. (Less than 5% of the diastereomer was observed). Oxidation using NMO and TPAP gave ketone **1.141** in 80% yield (Scheme 1.24). The relative stereochemistry was confirmed using nOe experiments. Next, the addition of methylmagnesium bromide to ketone **1.141** provided a mixture of **1.142** and **1.143** in an 8:1 ratio**,** favoring the desired isomer **1.142**.



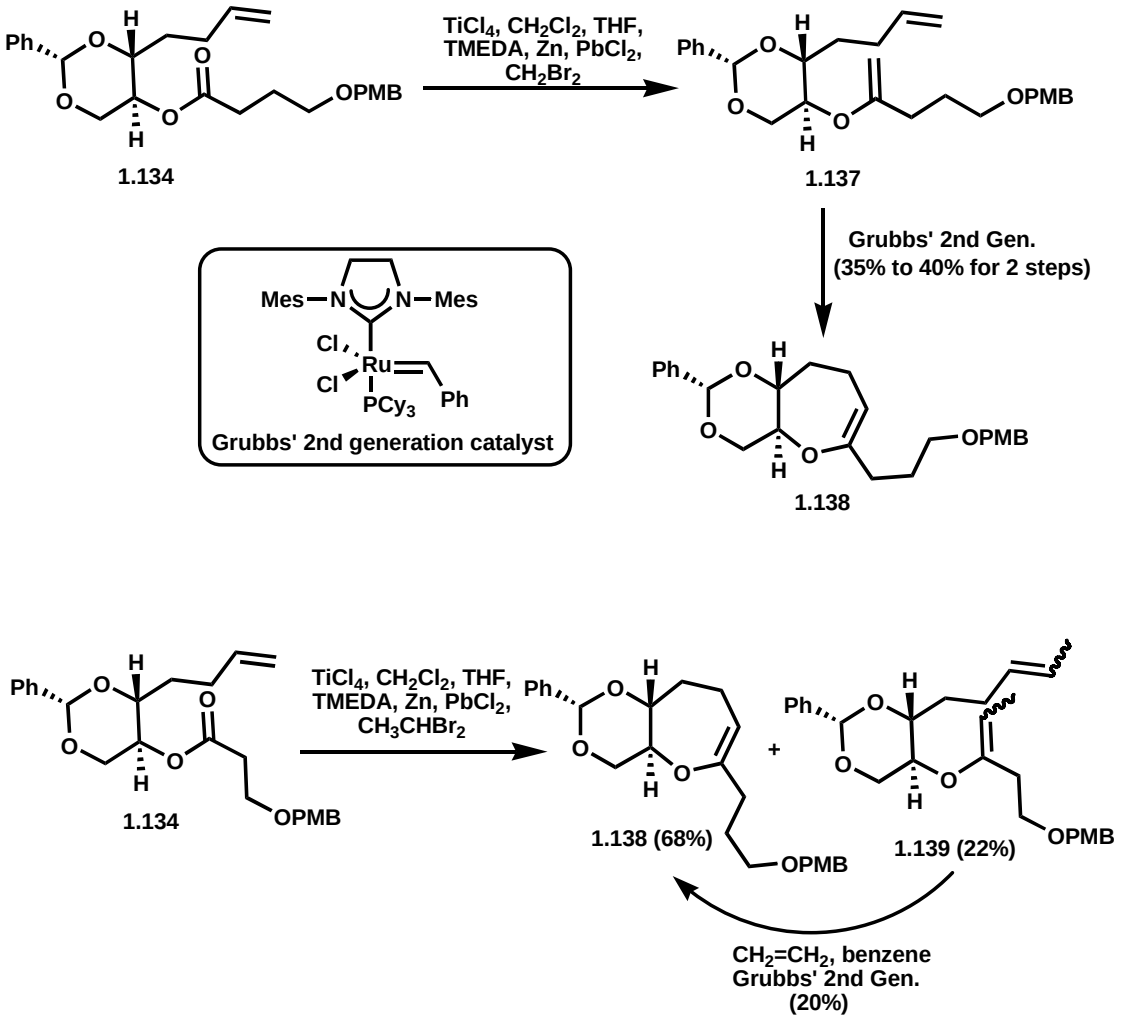
1.129 1.130 1.131 1.132 1.134 1.133

Scheme 1.21. Synthesis of olefinic-ester **1.133**

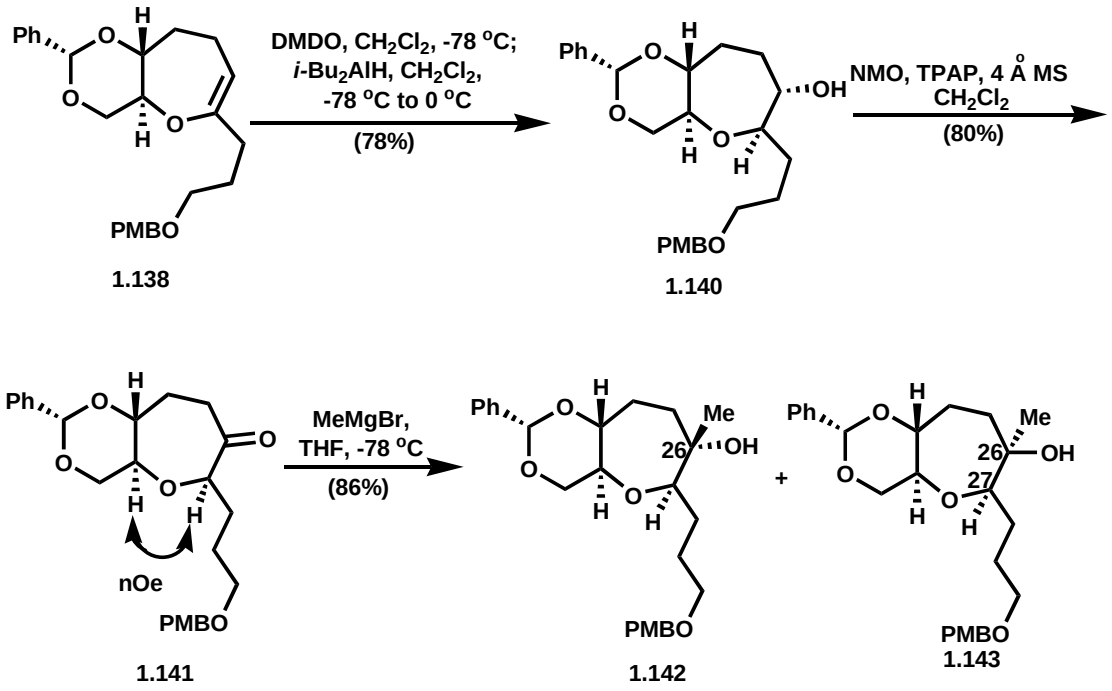


1.135 1.136 1.134

Scheme 1.22. Synthesis of 4-(4-methoxybenzyloxy)butanoic acid



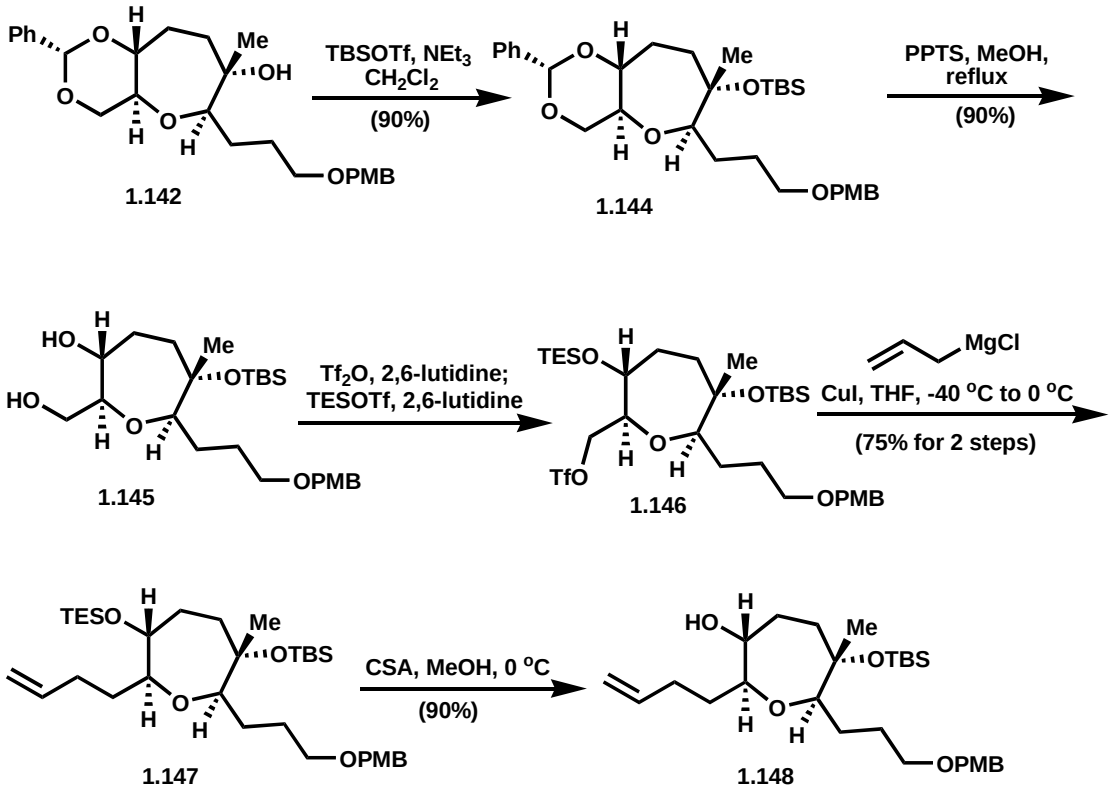
Scheme 1.23. Formation of the E-ring



Scheme 1.24. Generation of the tertiary alcohol at C-26

The relative stereochemistry at the C26 stereocenter of **1.143** was established by nOe correlations between the 26-Me and 27-H. The corresponding nOe correlations were not observed for **1.142**.

Tertiary alcohol **1.142** was protected as the corresponding TBS ether to give **1.144** in 90% yield. The acetal in **1.144** was deprotected using PPTS in methanol to give diol **1.145** in 90% yield. The generation of the primary triflate and the secondary TES ether was realized in one-pot to give **1.146**. Displacement of the triflate with allyl cuprate generated in situ afforded homoallyl derivative **1.147** in 75% yield over the two steps. Hydrolysis of the TES ether in acidic conditions gave E-ring alcohol **1.148** in 90% yield (Scheme 1.25).



Scheme 1.25. Synthesis of the E-ring alcohol

The AB-ring acid was synthesized as shown in Scheme 1.26. Starting from TBDPS protected aldehyde **1.149**, crotylation generated the desired alcohol **1.150**. Steglich esterification between **1.150** and known acid **1.103**[44] afforded olefinic-ester **1.151**. One-carbon homologation of the vinyl derivative **1.151** generated allyl derivative **1.152**. The olefinic-ester **1.152** was then subjected to the titanium ethylidene cyclization to obtain cyclic enol ether **1.153** in 75 % yield. Cyclic enol ether **1.153** was treated with DMDO followed by $AlMe_3$ to obtain secondary alcohol **1.154** in 65% yield. Using PPTS and pyridine, the B-ring was formed in two steps from **1.154**. Treatment of **1.155** with

DMDO followed by allylmagnesium chloride resulted in the allylated product **1.156** in 80% yield. In order to test our coupling strategy, we simplified the acid partner. The free alcohol in **1.156** was protected as the corresponding TES ether which was converted to acid **1.158** in two steps.

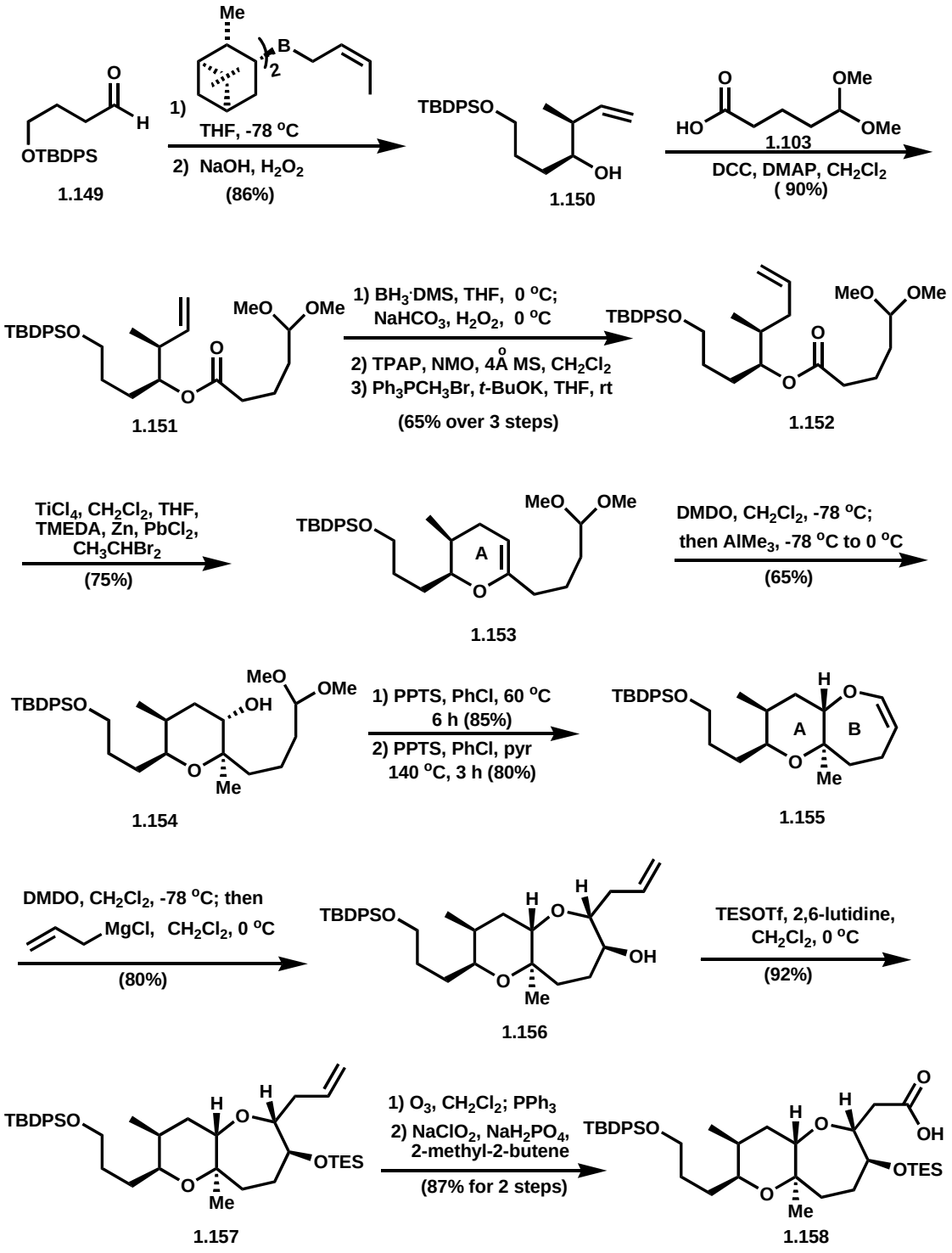
After getting the appropriate coupling partners **1.148** and **1.158**, Yamaguchi esterification brought the two pieces together (Scheme 1.27). With the ester in hand, olefinic-ester cyclization was attempted to give the brevenal D-ring. Unfortunately, the titanium ethylidene reagent gave acyclic enol ether **1.160** in 50% yield. Subjecting acyclic enol ether **1.160** to Grubbs' 2nd generation catalyst led to the decomposition of **1.160**. Methylenation and ring closing metathesis was also unsuccessful. Treatment of **1.159** with titanium methylidene reagent led to its decomposition (Scheme 1.28).

Third generation of brevenal

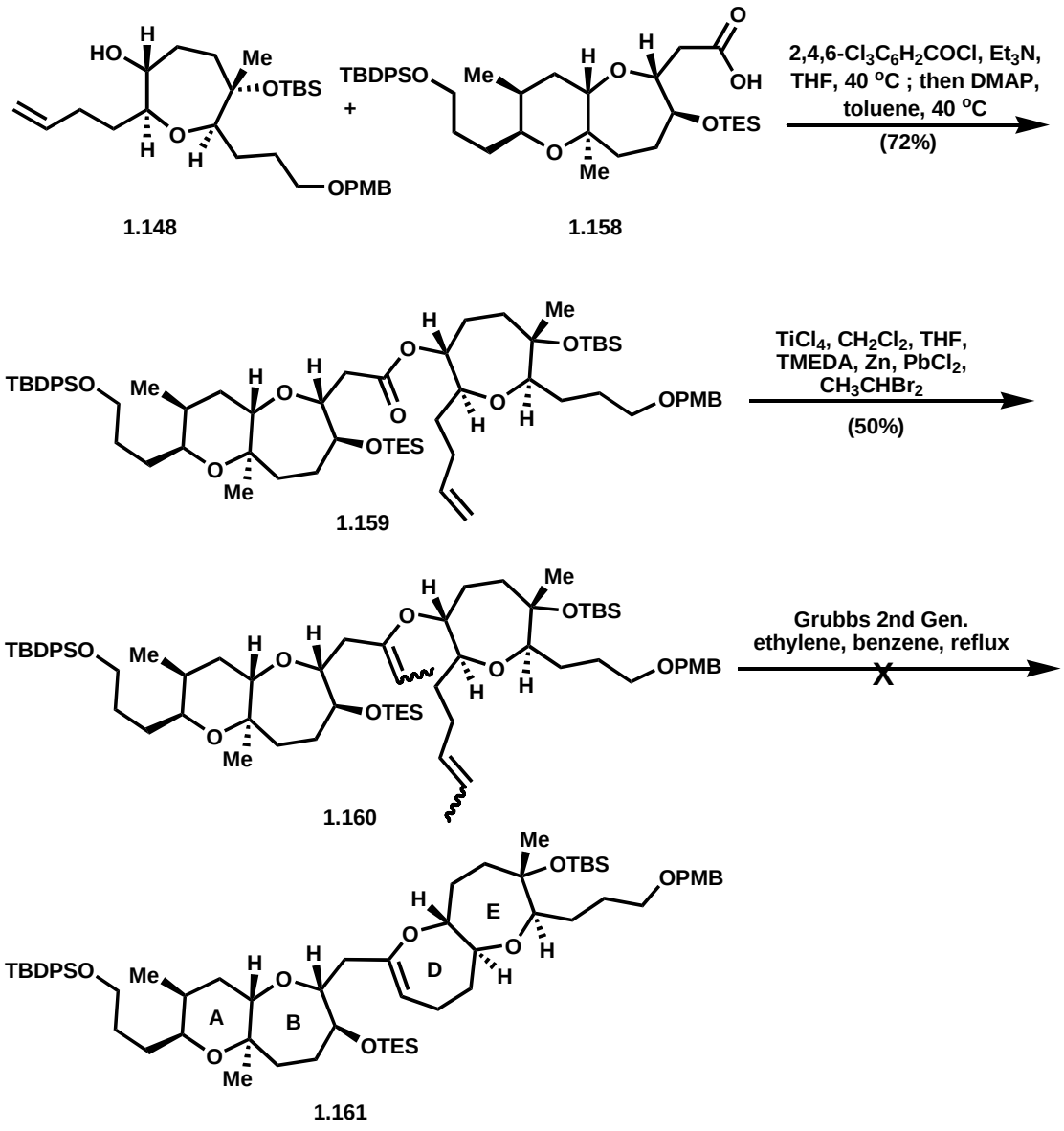
In order to circumvent the cycliztion problem, a modified coupling strategy was proposed (Scheme 1.29). Here, we plan to use an olefinic-ester cyclization to construct the C-ring. Disconnection of ester **1.164** leads to the AB-alcohol **1.165** and E-acid **1.166**.

In collaboration with Mr. John Rohanna, the AB-ring alcohol was synthesized from intermediate **1.156**. Oxidation using TPAP and NMO gave ketone **1.167** in 91% yield (Scheme 1.30). Rubottom oxidation of **1.167** installed the α-hydroxyl group as a TES protected ether. Deprotection of the TES group in **1.168** gave hydroxy-ketone **1.169**. Reduction of **1.169** with *i*Bu_2AlH gave *syn* diol **1.170** which was selectively protected as the corresponding C(14) benzyl ether **1.171** in 82% yield. The coupling partner E-ring

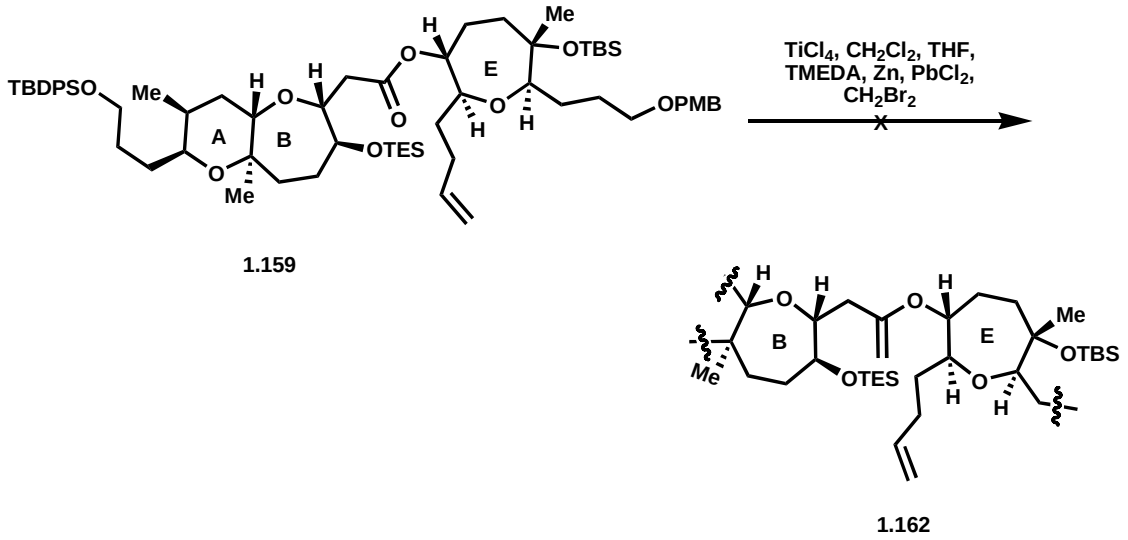
acid **1.172** was formed in three steps from the intermediate **1.147**, involving dihydroxylation, oxidative cleavage and Pinnick oxidation (Scheme 1.31).



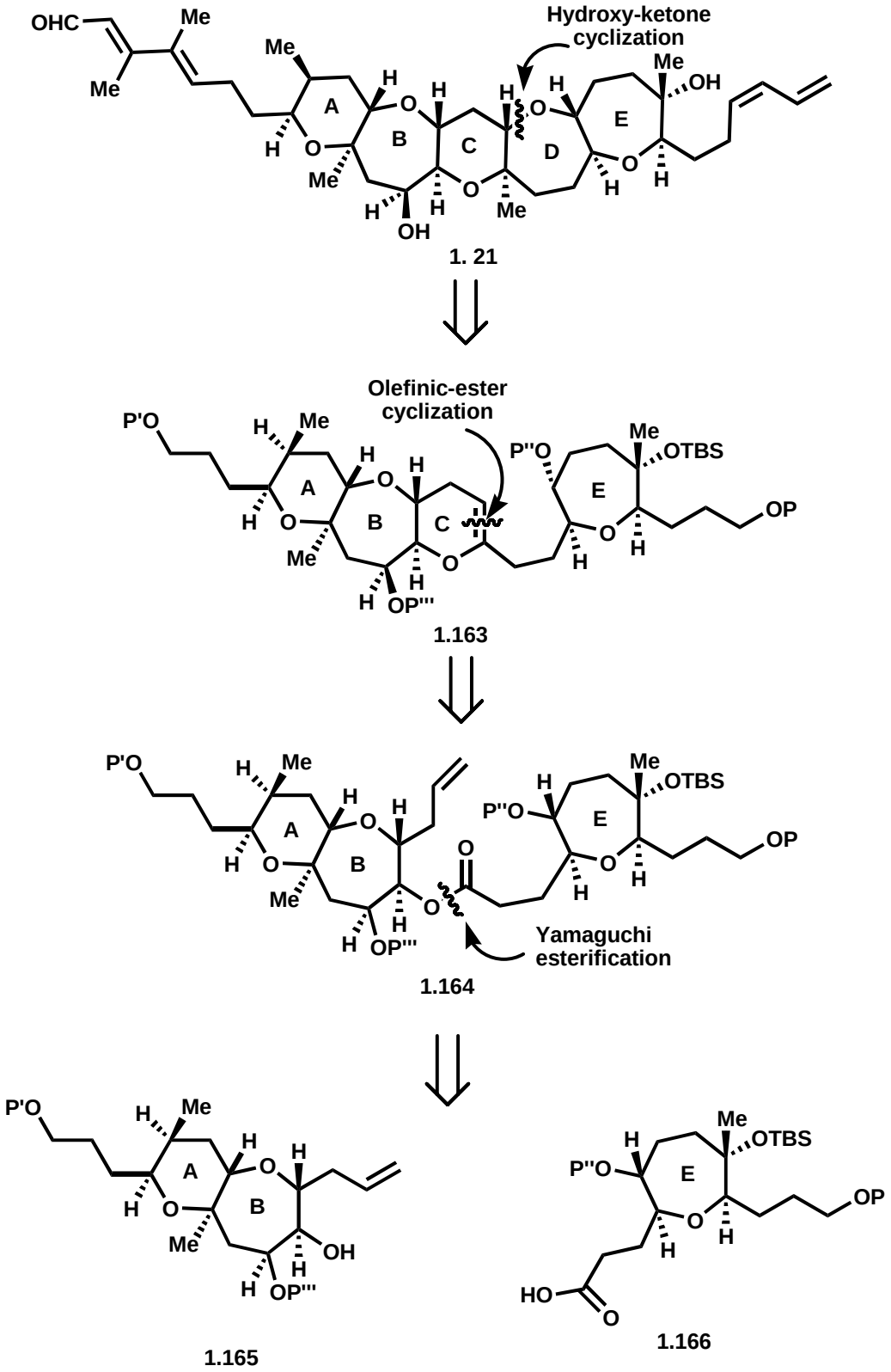
Scheme 1.26. Synthesis of the AB-ring acid



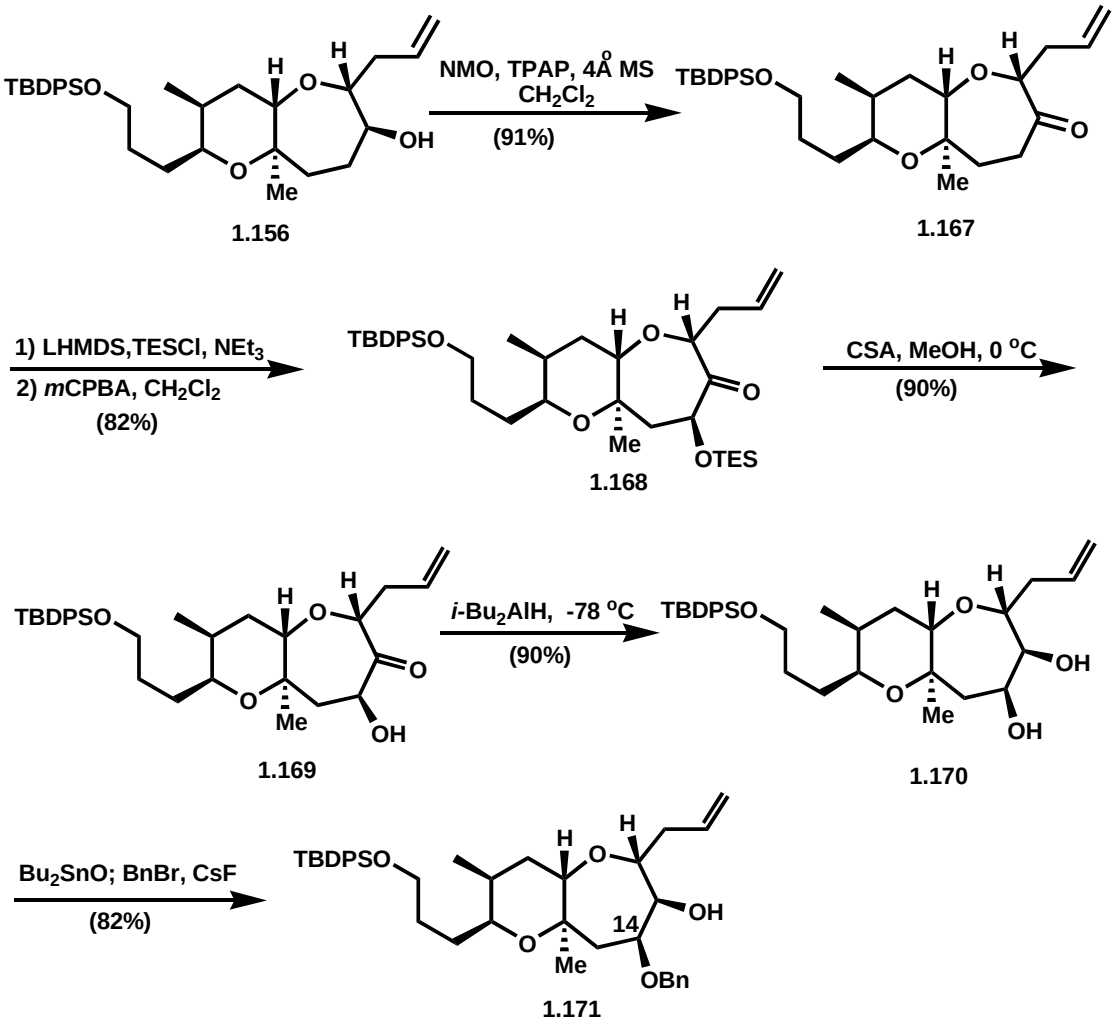
Scheme 1.27. Model studies of coupling strategy



Scheme 1.28. Initial attempt at D-ring formation

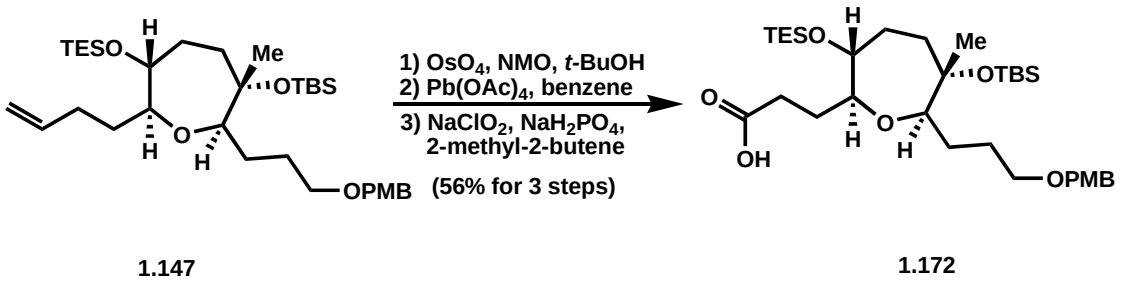


Scheme 1.29. Retrosynthetic analysis of brevenal



Scheme 1.30. Synthesis of the AB-ring alcohol

With both coupling partners in hand, we began to test our new coupling strategy (Scheme 1.32). Yamaguchi esterification between E-acid **1.172** and AB-alcohol **1.171** provided ester **1.173** in 76% yield. A Takai reaction constructed the C-ring smoothly to give **1.174** in 70% yield. The next step was the installation of the angular methyl group. However, the use of a DMDO epoxidation/$AlMe_3$ addition afforded a mixture of diastereomers **1.175** and **1.176** in a ratio of 1.3:1.



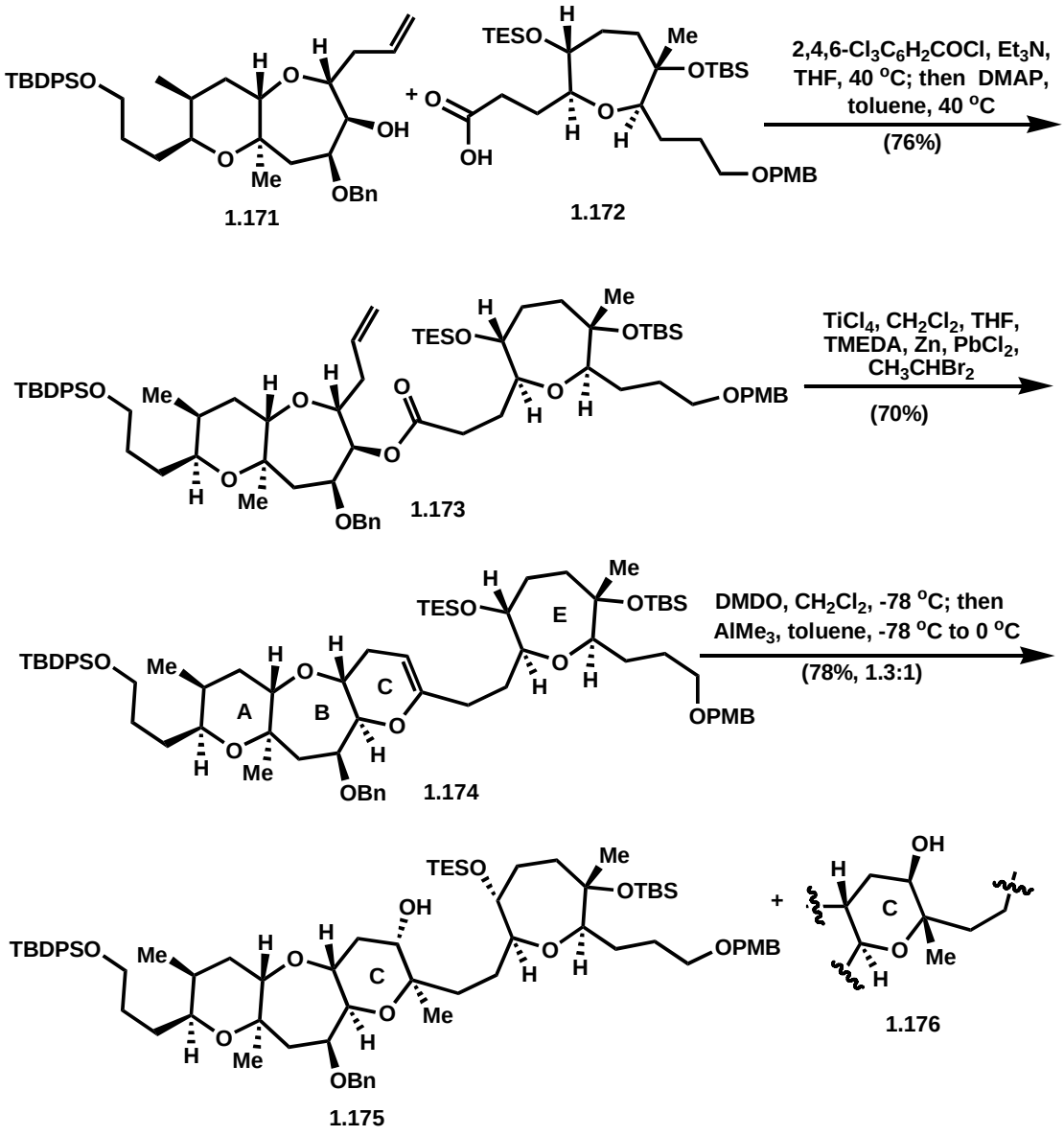
1.147 **1.172**

Scheme 1.31. Synthesis of E-ring acid

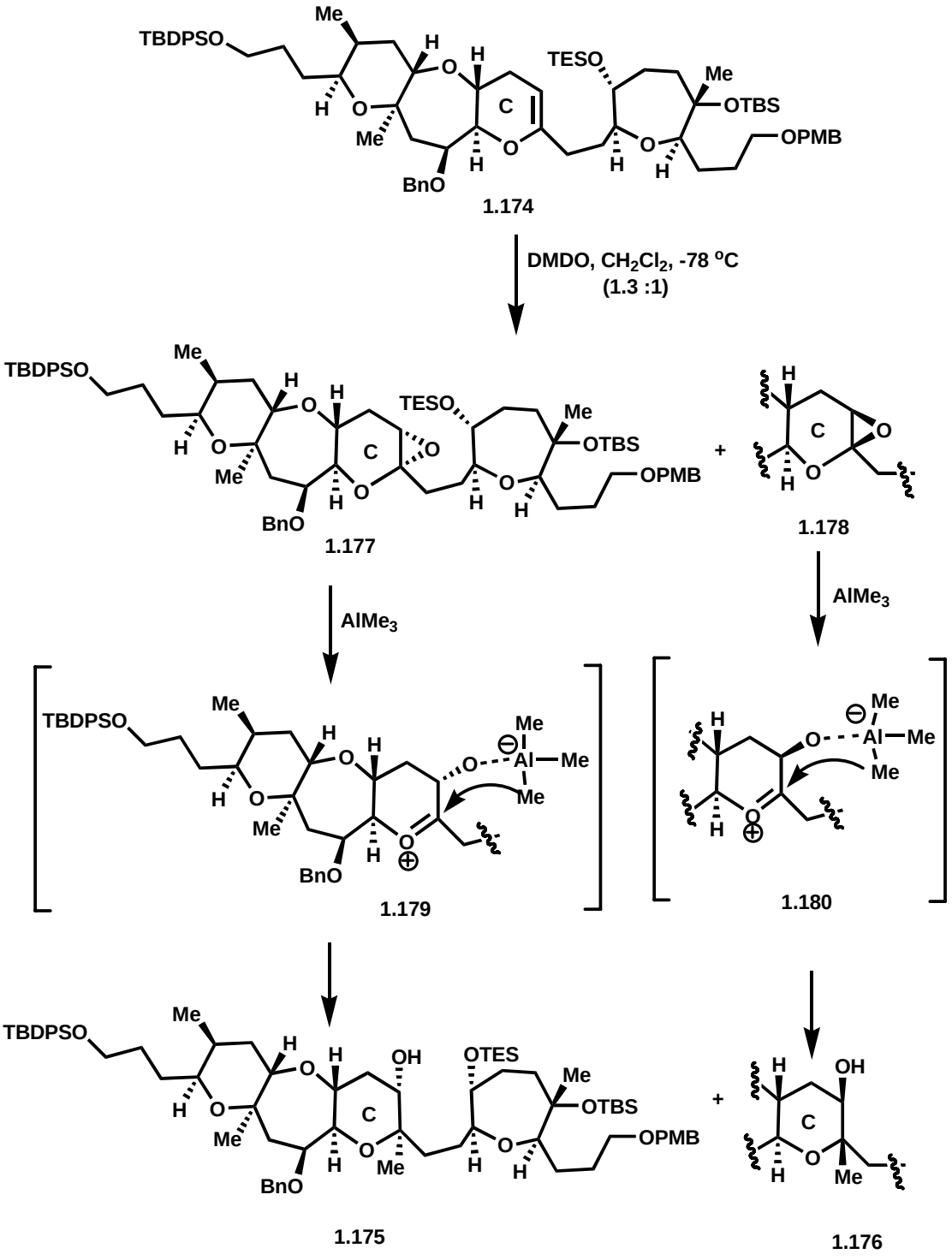
As a consequence of the mechanism for this transformation, the presence of a mixture resulted from a nonselective DMDO oxidation (Scheme 1.33). Since this was the late stage synthesis of brevenal, we felt this result was unacceptable and began to explore new conditions to take full use of the mixture of epoxides. In order to avoid the intramolecular transfer of the methyl group as proposed with intermediates **1.179** and **1.180**, we felt that the oxygen anion needed to be blocked.

In 2005, Scott Roberts reported the addition of ketene acetal **1.182** to epoxide **1.181** in the presence of TBSOTf to afford β-C-ketoside **1.183** in 77% as a single diastereomer (Scheme 1.34).[43] DFT calculations predicted that the low-energy conformer for the oxocarbenium **1.184** was a boat. The stereochemical outcome of the reaction could be explained by the approach of the nucleophile to the face of the oxocarbenium that was opposite the pseudoaxial TBS ether. Considering our strategy for the total synthesis of brevenal, we began considering the use of TBSOTf as Lewis acid in this transformation.

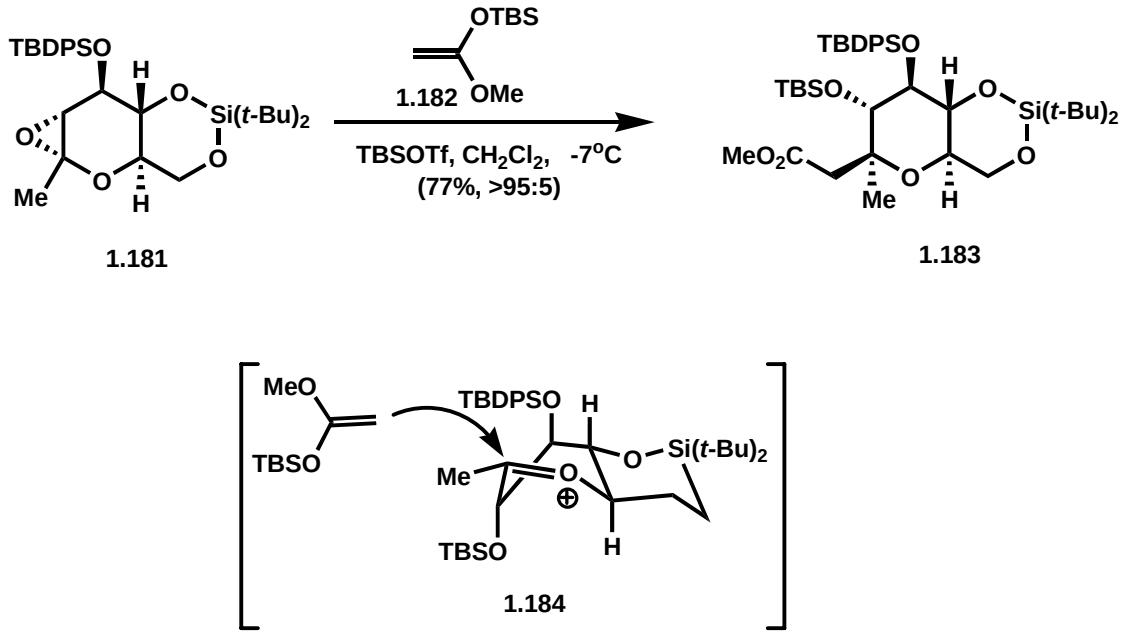
Alexander Wei's group carried out *syn* additions to 4α-epoxypyranosides using organozinc reagents (Table 1.1).[48(a)] The addition of RZnX species to 4α-epoxypyranosides proceeded with high selectivity *(syn: anti* > 20:1) for a variety of sp^2-



Scheme 1.32. Coupling between AB-alcohol and E-ring acid



Scheme 1.33. Installation of the angular methyl group on the C-ring of brevenal

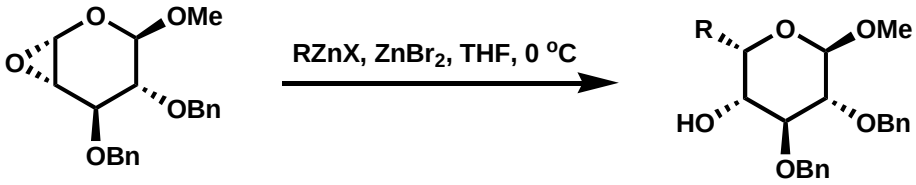


Scheme 1.34. Mukaiyama-type addition reaction with ketene acetal

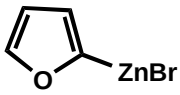
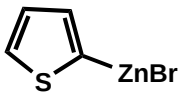
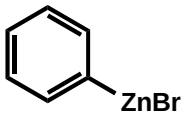
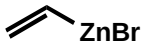
and sp-carbon nucleophiles, producing the corresponding L-idopyranoside derivatives in good to high yields. The most reliable *syn* additions were produced by generating RZnX species via the transmetallation of organolithium or Grignard reagents. The use of excess $ZnBr_2$ was important in this chemistry. Systematic examination of reaction conditions revealed that the presence of excess $ZnBr_2$ significantly improved the efficiency of addition.

Song Xue reported the zinc-mediated synthesis of α-C-glycosides from 1,2-anhydroglycosides.[48(b)] They demonstrated a new method for the synthesis of α-C-glycosides by using CF_3CO_2ZnR which was generated in situ from the reaction of ZnR_2 with CF_3CO_2H in CH_2Cl_2. Importantly, the reactions of functionalized zinc reagents with anhydroglycosides proceeded smoothly and were amenable to the presence of halides and esters as shown in Table 1.2.

Table 1.1. Wei's *syn* additions to 4α-epoxypyranosides



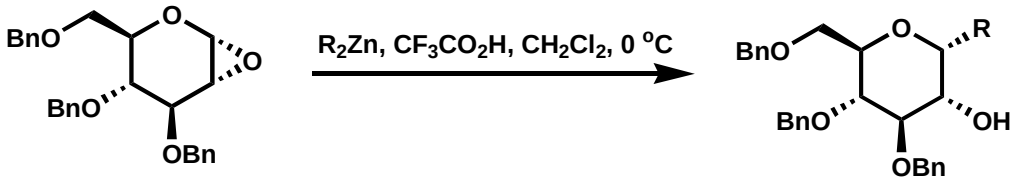
1.185

Entry	RZnX	Product	Yield (%)
1		**1.186**	84
2		**1.187**	74
3		**1.188**	80
4		**1.189**	69
5		**1.190**	77

Based on the previous work from our group[49] and the work outlined above[48], we proposed to use organozinc reagents as nucleophiles. Before attempting the chemistry on the real system, we began with two model systems as outlined below.

Beginning with tri-*O*-benzyl-D-glucal **1.198** as the initial model, epoxidation of **1.198** followed by the addition of dimethylzinc in the presence of TBSOTf generated α-C-glycoside **1.199** as a single diastereomer in 89% yield (Table 1.3, entry 1). In order to determine the stereochemistry of product **1.199**, the TBS group in **1.199** was removed with TBAF to give the known free alcohol **1.200** whose spectrum matched that published previously.[49(a)] However, the addition of dimethylzinc in the absence of TBSOTf only

Table 1.2. Xue's zinc-mediated synthesis of α-C-glycosides from 1,2-anhydroglycosides



1.191

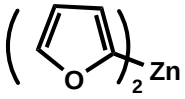
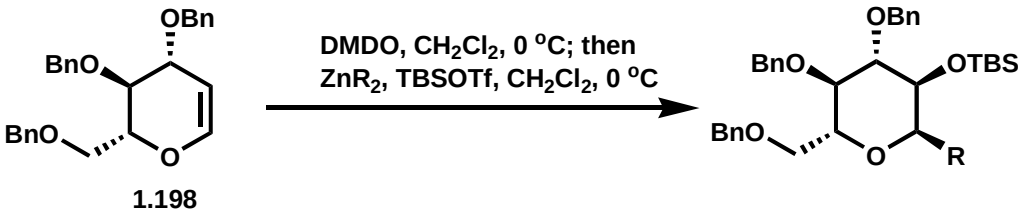
Entry	ZnR_2	Product	Yield (%)
1	$ZnMe_2$	**1.192**	81
2	$ZnEt_2$	**1.193**	65
3	$ZnPh_2$	**1.194**	64
4	$Zn(CH_2CH_2CH_2CH_2Cl)_2$	**1.195**	58
5	$Zn(CH_2CH_2CH_2CH_2OAc)_2$	**1.196**	53
6		**1.197**	82

Table 1.3. Dimethylzinc and diethylzinc as nucleophiles

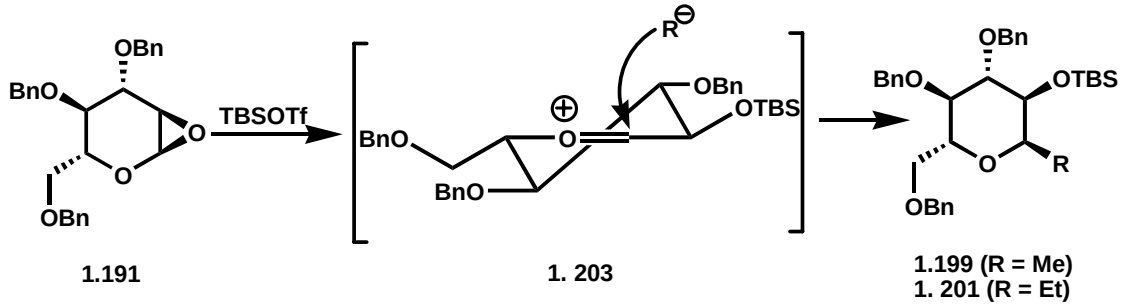


1.198

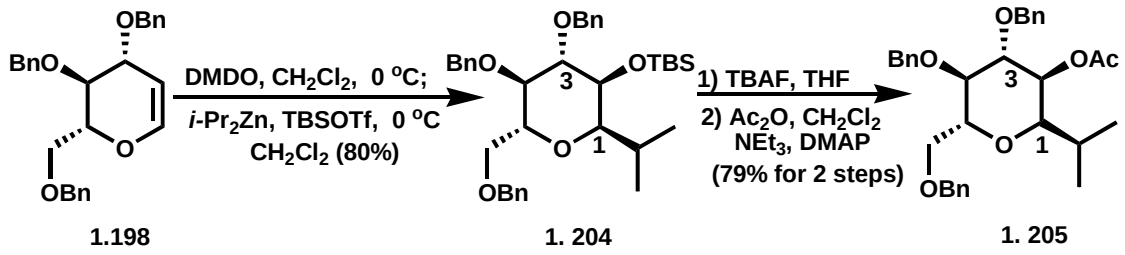
Entry	R	Products	Yield (%)
1	Me	**1.199**	89
2	Et	**1.201**	86

gave 30% of **1.200**. Diethylzinc gave a similar result, affording the corresponding addition products **1.201** in 86% (Table 1.3, entry 2). The stereochemistry of **1.201** was determined after conversion of **1.201** into the corresponding acetate **1.202** whose spectrum matched that reported previously.[48(b)] The stereochemical outcome for the generation of **1.199** and **1.201** was rationalized as illustrated in Scheme 1.35. Epoxide **1.191** reacts with TBSOTf to give oxocarbenium intermediate **1.203**. The nucleophile then attacks from the axial direction to give *syn* products **1.199** and **1.201**.

When $(i\text{-Pr})_2Zn$ was used in this reaction, α-isomer **1.204** was isolated in 80% yield (Scheme 1.36). The stereochemistry of **1.204** was determined by the $J_{1,3}$ values for H(1), H(2) and H(2), H(3) (ie. $J_{H(1),H(2)} = 4.4$ Hz, $J_{H(2),H(3)} = 7.3$ Hz). Interestingly, acetate **1.205** corresponding to **1.204** showed a different conformation as evidenced by its H(2) splitting pattern and coupling constant. The small $J_{1.3}$ values for H(1), H(2) and H(2), H(3) (i.e. $J = 3.42$ Hz) implied a boat conformation for acetate **1.205**.



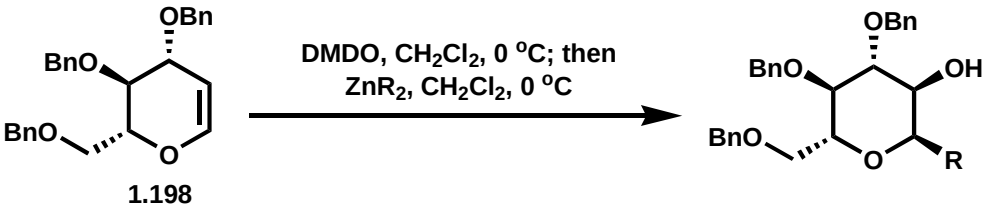
Scheme 1.35. Rationalization of the stereochemical outcome



Scheme 1.36. Diisopropylzinc as a nucleophile

In addition to the sp^3-carbon nucleophiles, the zinc chemistry was also applicable to the coupling of sp^2-carbon nucleophiles with **1.198** (Table 1.4). Divinylzinc which came from the metathesis reaction between vinyl magnesium chloride and zinc chloride, reacted with the epoxide from **1.198** to give **1.206** as a single diastereomer in 75% yield. Interestingly, in contrast to the sp^3 nucleophiles, no TBSOTf was necessary in this reaction. We believe that this is due to the presence of excess magnesium salts that serve to active the epoxide. Diphenylzinc, which came from the reaction between phenyl magnesium chloride and zinc chloride, provided a similar result. Phenyl adduct **1.207** was generated as a single diastereomer in 72% yield. When commercial diphenylzinc was used in this reaction, no phenyl adduct **1.207** was observed regardless of the presence of TBSOTf. The only product from this reaction was the diol which came from hydrolysis

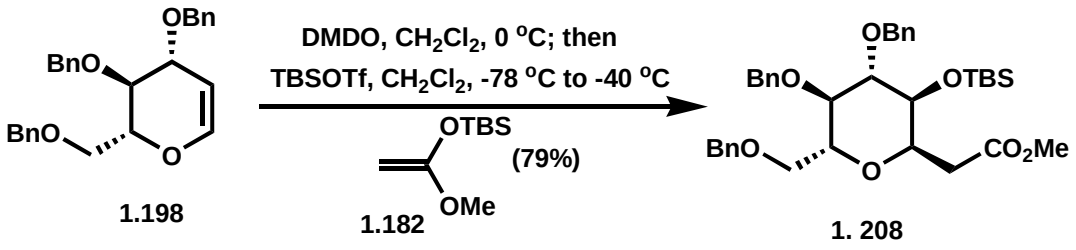
Table 1.4. Addition of sp^2- hybridized carbon nucleophiles



Entry	R	Products	Yield (%)
1	vinyl	**1.206**	75
2	phenyl	**1.207**	72

of **1.191** during workup. The low solubility of commercial diphenylzinc in solvents such as THF, CH_2Cl_2, ether and toluene might be the reason for the observed discrepancy.

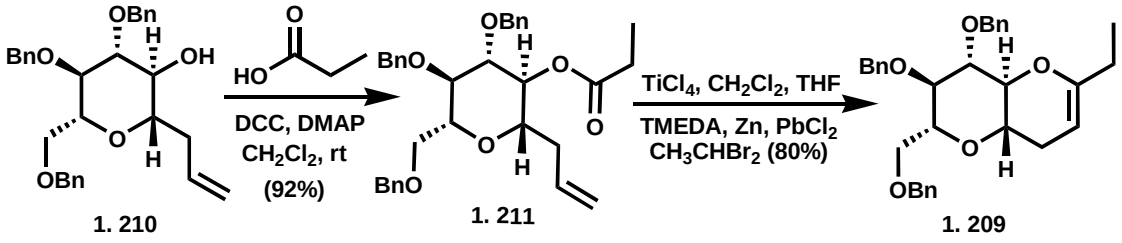
In addition to zinc reagents, ketene acetal **1.182** was used as a nucleophile as shown in Scheme 1.37. The addition of **1.182** to epoxide **1.191** in the presence of TBSOTf afforded *syn*-addition product **1.208** in 79% yield.



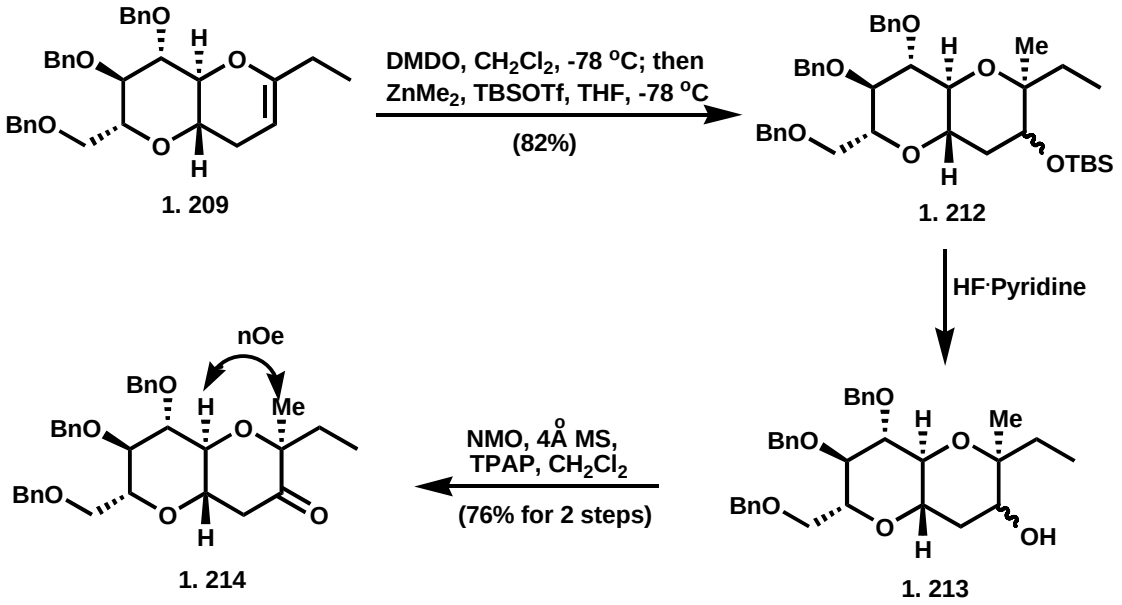
Scheme 1.37. Ketene acetal as a nucleophile

Encouraged by the preliminary results using tri-*O*-benzyl-D-glucal, we sought a more complex model system and chose **1.209**, whose epoxidation chemistry would more closely match that of our brevenal substrate in that it would not be diastereoselective. Enol ether **1.209** was prepared in two steps from known compound **1.210** (Scheme 1.38). Esterification between **1.210** and propanoic acid afforded ester **1.211** in 92% yield. Olefinic-ester cyclization using the titanium ethylidene reagent generated cyclic enol ether **1.209** in 80% yield.

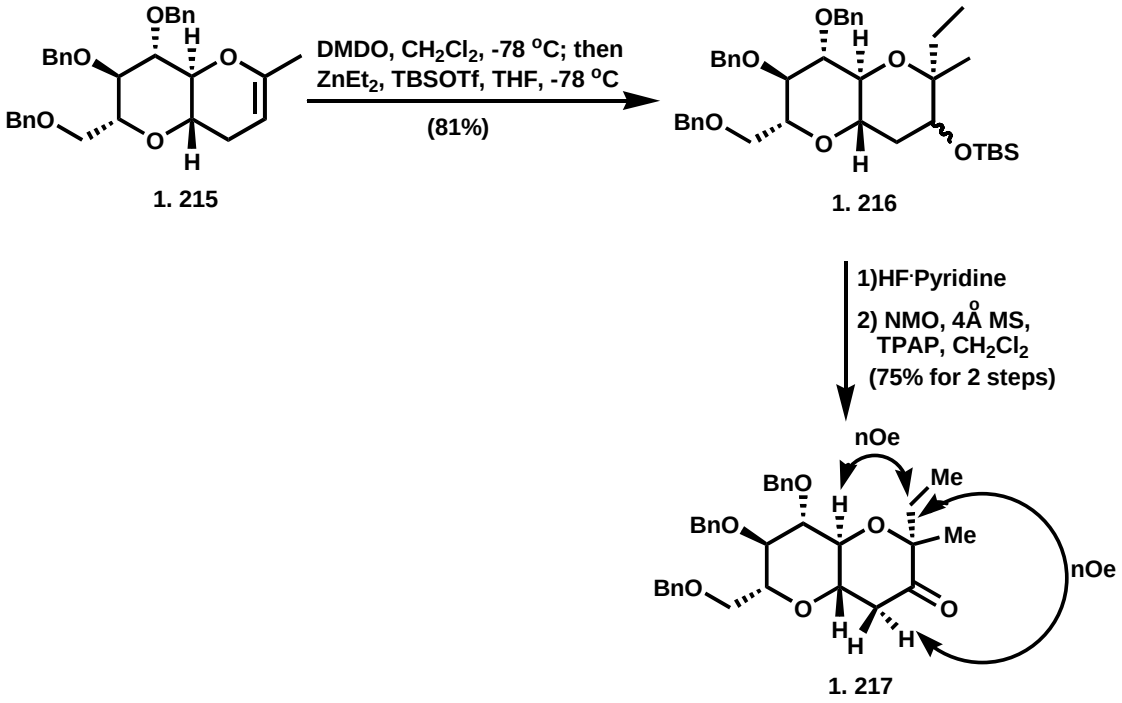
Epoxidation of **1.209** followed by the addition of $ZnMe_2$ in the presence of TBSOTf afforded **1.212** as a 1.2:1 mixture of silyl ethers in 82% yield. Deprotection of **1.212** followed by oxidation generated ketone **1.214** as a single diastereomer in 76% yield for the two steps (Scheme 1.39). The stereochemistry of **1.214** was established using nOe experiments. These data support our hypothesis regarding axial addition of the organozinc reagents regardless of the stereochemistry of the epoxide. In a similar fashion, we also synthesized **1.216** and **1.217** using Et_2Zn in the coupling reaction (Scheme 1.40).



Scheme 1.38. Synthesis of enol ether **1.197**



Scheme 1.39. Addition of $ZnMe_2$ to bicyclic enol ether **1.209**

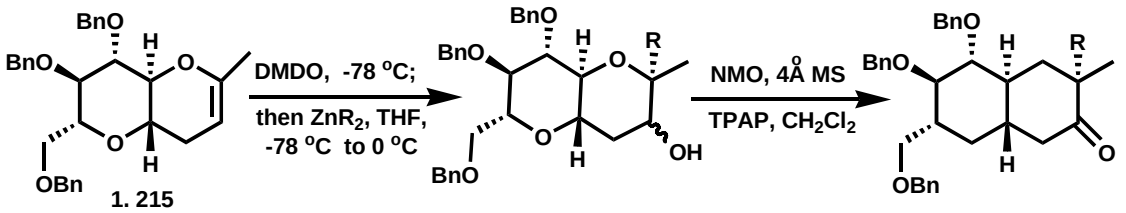


Scheme 1.40. Addition of $ZnEt_2$ to bicyclic enol ether **1.215**

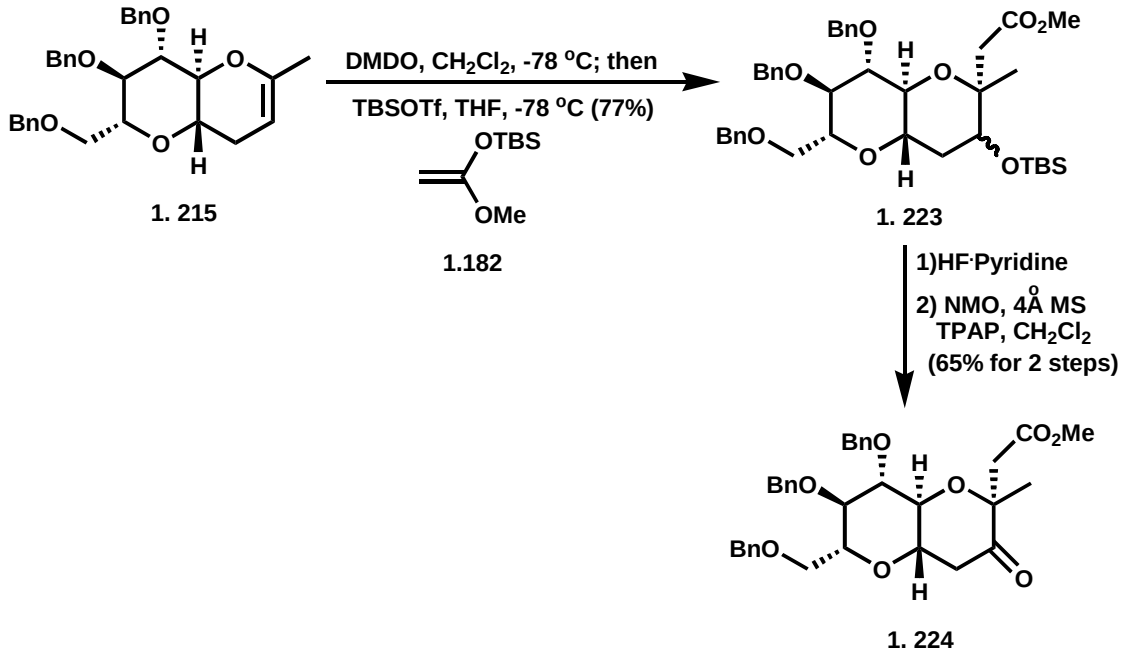
We next examined the reactions with sp^2-hybridized carbon nucleophiles. The addition of divinylzinc to the epoxides from **1.215** afforded **1.219** as a single diastereomer after oxidation (Table 1.5, entry 1). The stereochemistry for **1.219** was established by nOe experiments. In a similar fashion, the addition of diphenylzinc also gave ketone **1.221** as a single diastereomer after oxidation (Table 1.5, entry 2). In order to determine the stereochemistry of **1.221**, the benzyl groups were removed and the triol was converted to its corresponding acetate **1.222**.

Ketene acetal **1.182** was added to the mixture of epoxides from **1.215** to give ketone **1.224** as a single diastereomer after deprotection and oxidation (Scheme 1.41).

Table 1.5. Addition of sp^2- hybridized carbon nucleophiles

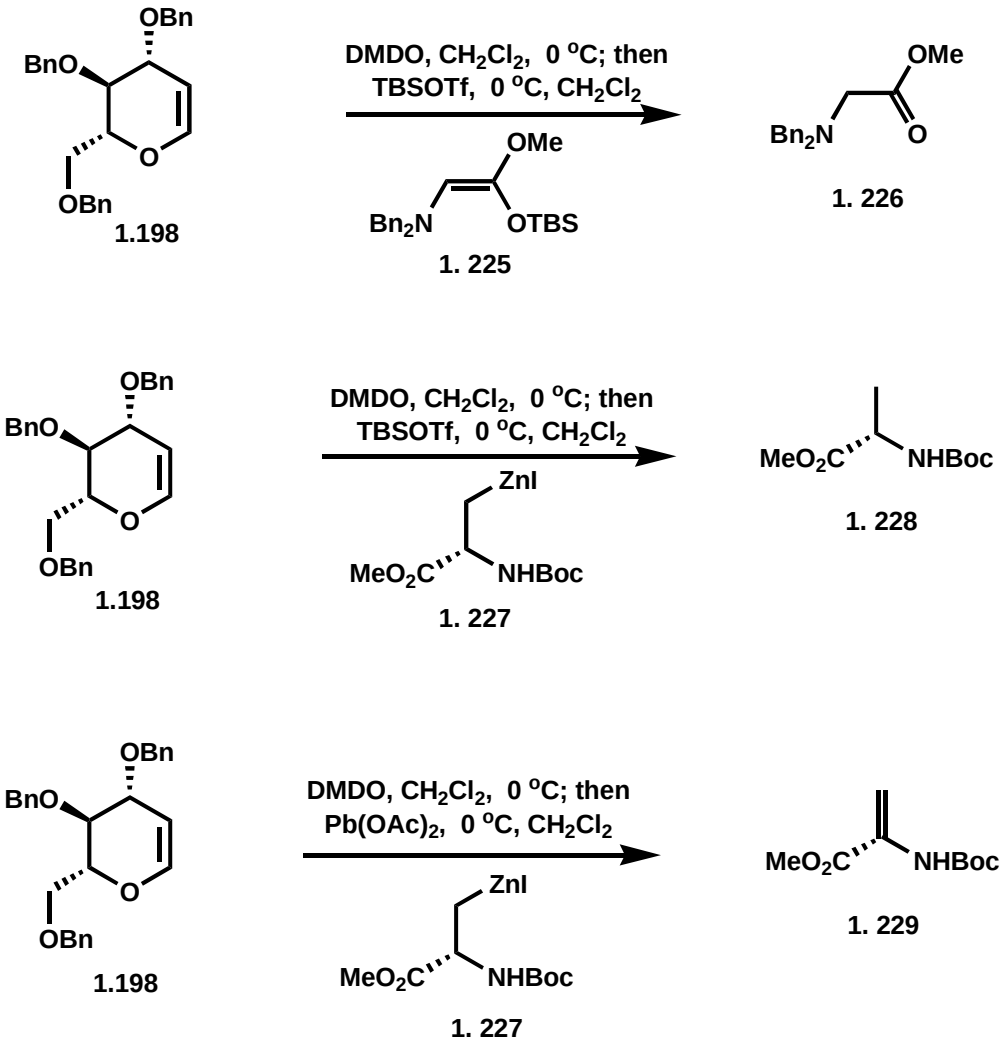


Entry	R	Alcohol	Yield (%) (DMDO/ZnR_2)	Products	Yield (%) (Oxidation)
1	vinyl	**1.218**	75	**1.219**	90
2	phenyl	**1.220**	68	**1.221**	86



Scheme 1.41. Ketene acetal addition to epoxides from **1.215**

Encouraged by the results from ketene acetal **1.182**, we studied the reaction using glycine-derived silyl enolate **1.225**[50] as a nucleophile (Scheme 1.42). The reaction between **1.198** and **1.225** led to products **1.226** which came from the hydrolysis of **1.225** and diol which came from the opening of epoxide **1.191** during workup. Longer reaction time or high temperature gave the same result. Serine-derived organozinc compound **1.227**[51] has been widely employed in palladium catalyzed cross-coupling reaction.[52] When **1.227** was used as a nucleophile in our coupling chemistry, **1.228** which came from the protonation during workup was isolated together with diol from **1.198**. In addition, when $Pd(OAc)_2$ was employed instead of TBSOTf, **1.229** which came from the β-elimination of the palladium intermediate was observed.

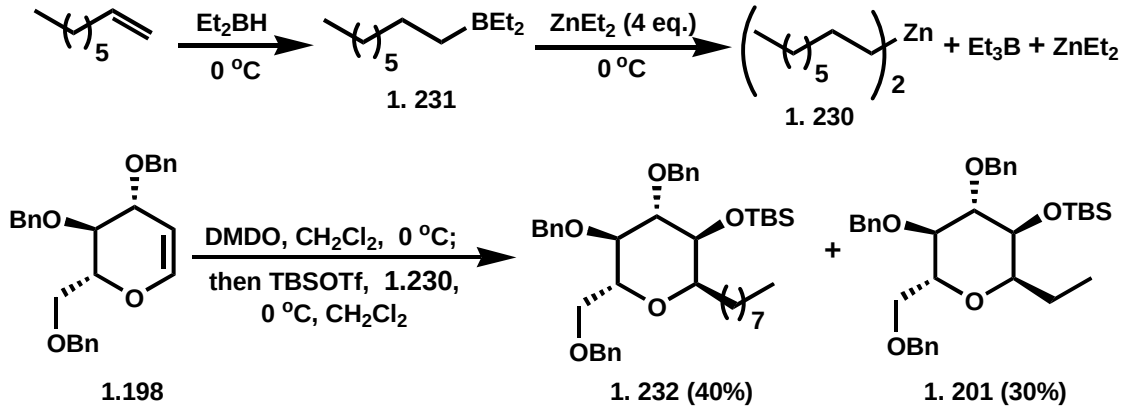


Scheme 1.42. Glycine-derived and serine-derived nucleophiles

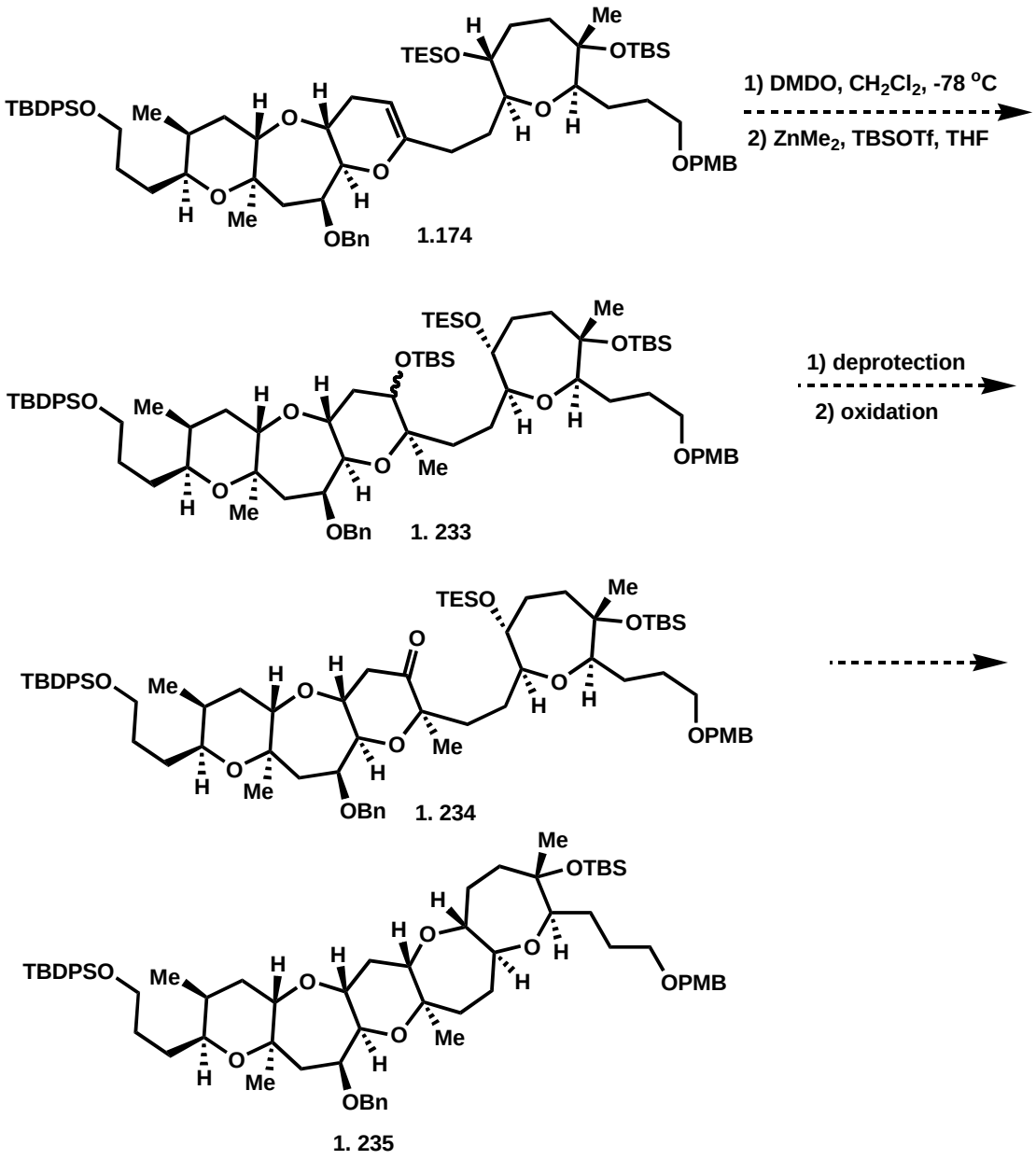
One of the limitations of this zinc chemistry is the source of the organozinc reagents. There are few commercially available organozinc reagents. So a general preparation of functionalized dialkylzinc is necessary. For simple organozinc reagents such as divinylzinc and diphenylzinc which were used in Table 1.4 and 1.5, the transmetalation of lithium or magnesium organometallics with zinc salts has been used frequently. Functionalized dialkylzinc substrates can be prepared from boron-zinc

exchange, which was developed by Paul Knochel and co- workers.[53] We started with a simple known substrate **1.230**.[53] Hydroboration of 1-octene with Et_2BH afforded **1.231**. Then **1.231** underwent a boron-zinc exchange with Et_2Zn to give a mixture of **1.230**, Et_3B and $ZnEt_2$. The excess $ZnEt_2$ and newly formed Et_3B could be pumped off under high vacuum (Scheme 1.43). However, it is hard to remove $ZnEt_2$ completely. **1.232** was isolated in 40% yield together with 30% of **1.201**. In order to remove $ZnEt_2$ completely, we tried higher temperature and longer time under high vacuum which led to the decomposition of the zinc reagents.

In summary, the use of DMDO/$ZnMe_2$ and TBSOTf would generate the axial addition product enabling us to overcome the lack of selectivity in the epoxidation reaction (Scheme 1.44). After deprotection and oxidation, products **1.233** would give ketone **1.234**. Cyclization of **1.234** would then give the brevenal pentacyclic core **1.235**.



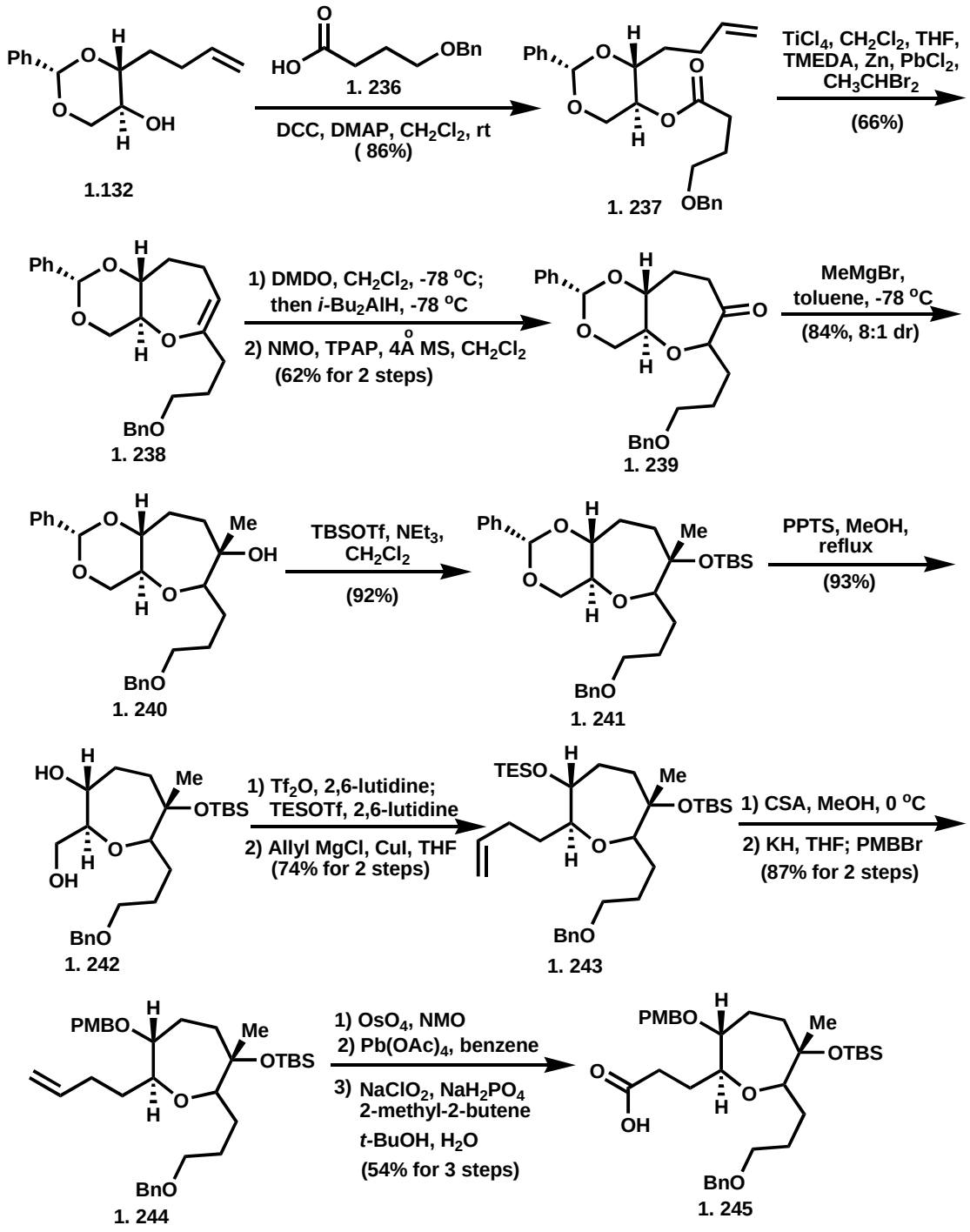
Scheme 1.43. Dialkylzinc via a boron-zinc exchange



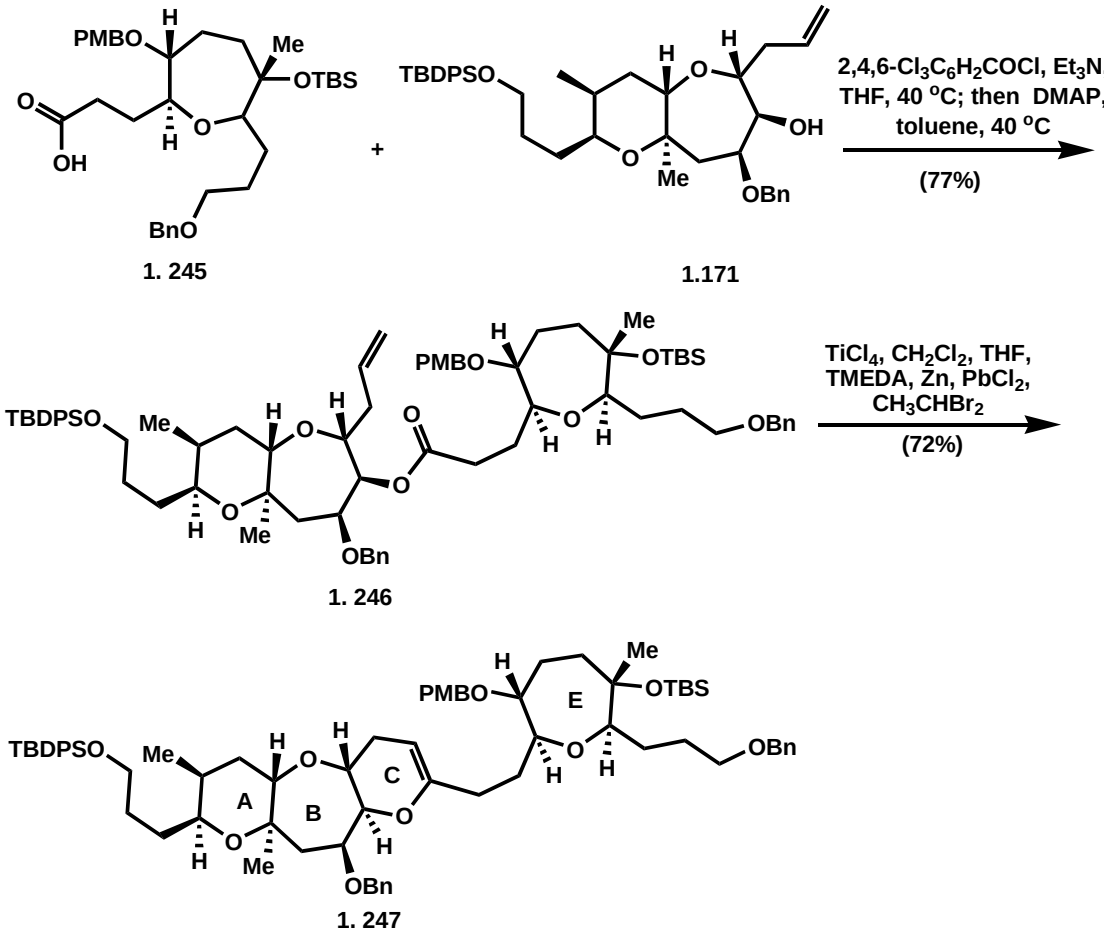
Scheme 1.44. Plan for synthesis of pentacyclic core

The synthesis of the requisite acid commenced with intermediate **1.132**. Esterification with alcohol **1.132** afforded olefinic-ester **1.237** in 82% yield. Treatment of **1.237** with the titanium ethylidene reagent afforded oxepene **1.238** in 65% yield**.** Oxepene **1.238** was subjected to DMDO followed by iBu$_2$AlH to generate ketone **1.239** after TPAP and NMO oxidation. Methylmagnesium bromide addition gave tertiary alcohol **1.240** as an 8:1 mixture favoring the desired diastereomer**.** After protecting group manipulation and allyl cuprate displacement of the primary triflate from **1.242**, **1.240** was converted into **1.243**. The TES group was removed and the alcohol was protected as the corresponding PMB ether **1.244**. The completion of the synthesis of the coupling partner **1.245** involved oxidative cleavage of the alkene and Pinnick oxidation (Scheme 1.45).

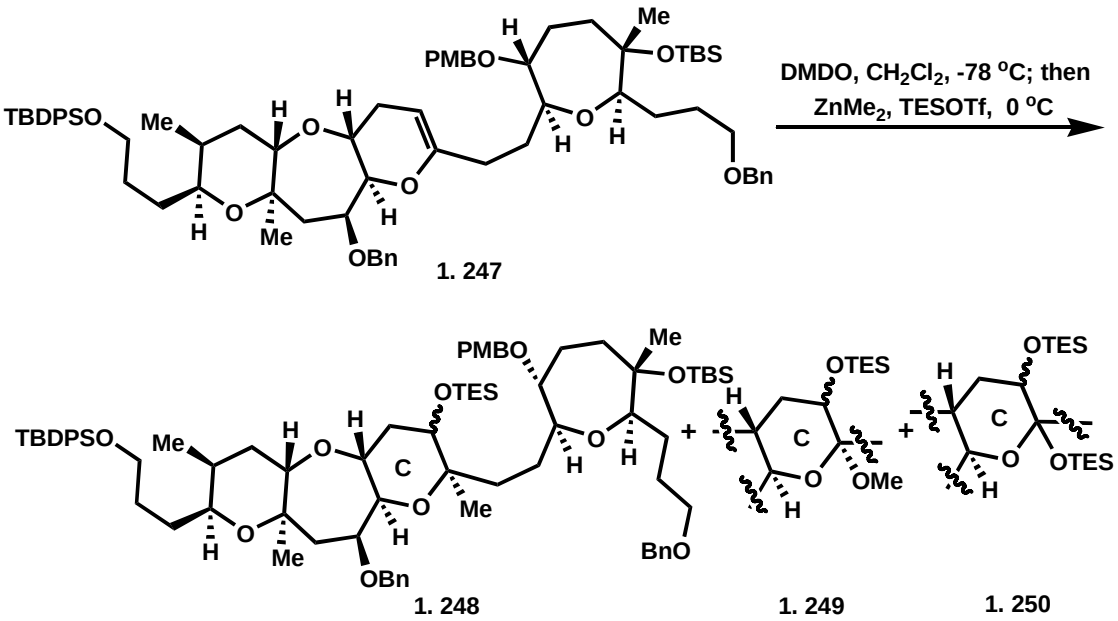
With **1.245** in hand, the coupling strategy was tested as described in Schemes 1.46 and 1.47. Yamaguchi esterification between **1.171** and **1.245** afforded ester **1.246** in 77% yield. Olefinic-ester cyclization gave C-ring enol ether **1.247** in 70% yield. The next step involved the installation of angular methyl group on the C-ring. Treatment of **1.247** with DMDO/ZnMe$_2$ and TESOTf generated the desired product **1.248** together with between 20% and 50% of **1.249** and **1.250** (Scheme 1.47). We believe that **1.249** is the result of methoxy group addition to the epoxide from **1.247** instead of the methyl group and that it results from the presence of Zn(OMe)R. The non reproducible results with ZnMe$_2$ forced us to explore other conditions. These experiments are being carried out currently by Yuan Zhang (Scheme 1.48). Enol ether **1.247** was converted to thioacetal **1.251** via epoxide intermediates. The resulting hydroxyl groups were protected as TES ethers and the thiol groups were converted to a methyl group using Zn(OTf)$_2$ and ZnMe$_2$. Deprotection followed by oxidation using TPAP and NMO gave a single diastereomer **1.253**.



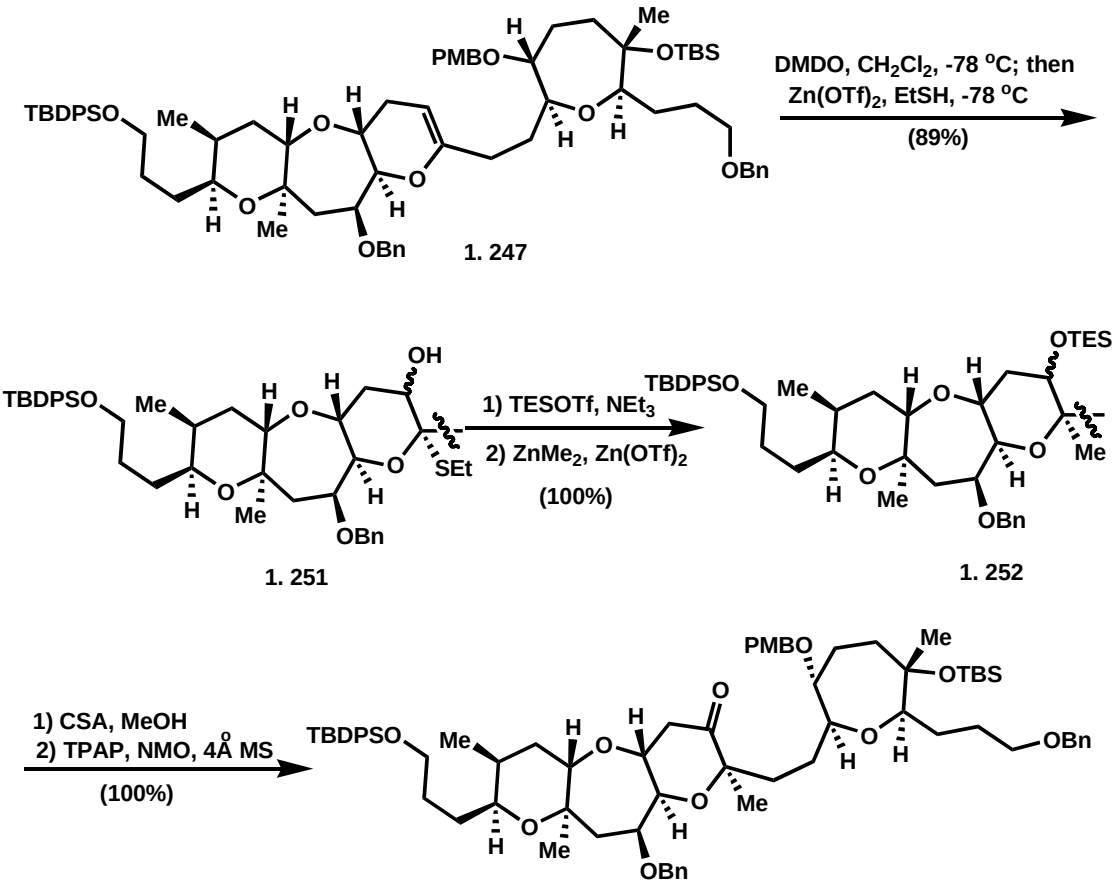
Scheme 1.45. Synthesis of E-ring acid **1.245**



Scheme 1.46. Coupling between AB-alcohol and E-ring acid



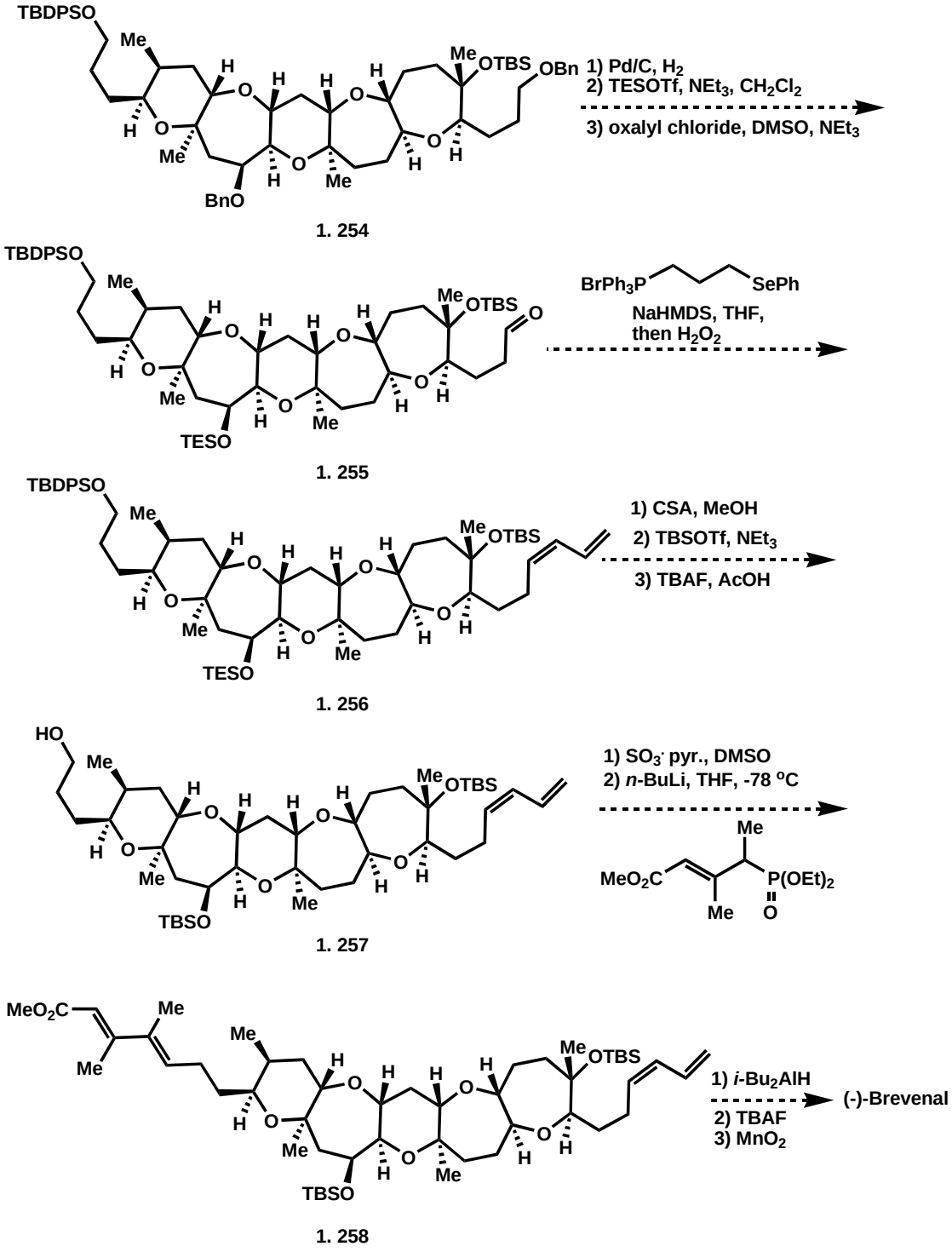
Scheme 1.47. Attempts to install the angular methyl group



Scheme 1.48. Attempts to install the angular methyl group by Yuan Zhang

Illustrated in Scheme 1.49 is our proposed completion of brevenal. Upon completion of the pentacyclic core **1.254**, the side chains would be installed following Yamamoto's protocol.[37] Protecting group manipulation and oxidation of the primary TES ether by Swern oxidation would afford aldehyde **1.255**. Wittig reaction followed by oxidation would install the right-hand side chain to give **1.256**. After protecting group manipulations, **1.256** would be converted to primary alcohol **1.257**. The left-hand side chain would be constructed by the Horner-Wadsworth-Emmons reaction of aldehyde from **1.257**. With **1.258** in hand, oxidation state manipulations on the allylic ester and global deprotection would give brevenal.

In summary, this chapter described our efforts towards the total synthesis of brevenal. In the first generation, a C-glycoside and enol ether ring closing metathesis centered strategy was used to construct the enantiomer of the C-E ring system of brevenal. In the second generation, disconnection of brevenal at the CD ring junction led to a more convergent strategy. The key transformations of the synthesis of the AB ring and the E ring include a one-step olefinic-ester cyclization and DMDO/nucleophile addition to form C-glycosides. Compared to Sasaki and Yamamoto's work, our linear steps would be shorter. In addition, our strategy is more convergent, flexible and amenable to analog synthesis. Compared to Crimmins' approach which is relied on aldol reactions of chiral oxazolidinones to introduce chiral centers, our synthesis used few chiral reagents. Most of the stereocenters were generated from the selectivity of the molecular itself. Overall, we believe this approach would lead to an efficient synthesis of brevenal and its analogs which can be used in the structure-activity relationship study.

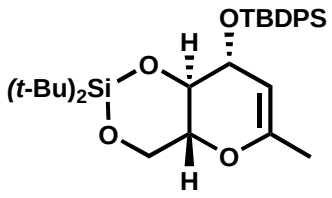


Scheme 1.49. Proposed plan for the completion of brevenal

Experimental Section

NMR spectra were recorded on either a Varian Inova-500 MHz or a Varian VXR-500 MHz spectrometer. Chemical shifts were reported in δ, parts per million (ppm), relative to benzene (7.15) or chloroform (7.25) as internal standard. Coupling constants, J, were reported in Hertz (Hz) and refer to apparent peak multiplicities and not true coupling constants. Optical rotations were obtained on a Perkin Elmer Model 343 polarimeter (Na D line) using a microcell with a 1 decimeter path length. Specific rotations ($[\alpha]^D$, Unit: $°cm^2/g$) are based on the equation $[\alpha]^D = (100\alpha)/(l \cdot c)$ and are reported as unitless numbers where the concentration *c* is in g/100 ml and the path length *l* is in decimeters. Specific rotations are reported as an average of 10 recordings with an integration time of 5 seconds for each recording. Mass spectra were recorded at the Mass Spectrometry Facility at the Department of Chemistry of the University of Utah at Salt Lake City on a Finnigan MAT 95 mass. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Solvents were purified according to the guidelines in Purification of Common Laboratory Chemicals (Perrin, Armarego, and Perrin: Oxford, 1966). THF, ether, benzene and toluene were distilled from sodium/benzophenone. CH_2Cl_2, DMSO, NEt_3, $(i\text{-}Pr)_2NEt$, TMEDA, MeOH, and CH_3CN were distilled from CaH_2. Zn dust (<10 μm, Aldrich) was activated by sequentially washing with HCl, H_2O, ether, and acetone and then drying under vacuum overnight. All other reagents were used without purification. Unless otherwise stated, all reactions were run under an atmosphere of dried nitrogen in flame-dried glassware. Concentration refers to removal of solvent under reduced pressure (house vacuum at ca. 20 mmHg). Compounds were named using Cambridgesoft's Chemdraw or conventional abbreviations.

Characterization



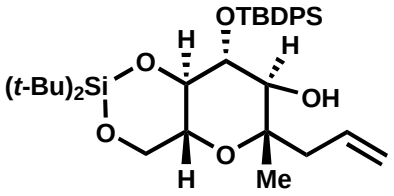
1. 94

(4aR,8R,8aR)-2,2-di-tert-butyl-8-(tert-butyldiphenylsilyloxy)-6-methyl-4,4a,8, 8a-tetrahydropyrano[3,2-d][1,3,2]dioxasiline (1.94). To a solution of MeOH (100 mL) and tri-*O*-acetyl-D-glucal **1.90** (19.0 g, 69.9 mmol) at rt was added K_2CO_3 (3.66 g, 20.5 mmol). The reaction mixture was stirred at rt for 3 d. Concentration and chromatography (CH_2Cl_2:MeOH, 6:1) provide **1.91** (10.0 g, 98%) as a colorless oil.

To a solution of D-glucal **1.91** (6.76 g, 46.3 mmol) in DMF (185 mL) at –40 ^oC was added $t Bu_2Si(OTf)_2$ (17.0 mL, 52.5 mmol) dropwise over 15 min. The solution was stirred for an additional 0.5 h. Pyridine (4.46 mL, 55.0 mmol) was added and the solution was stirred for 5 min. The solution was diluted with ether (500 mL). The phases were separated. The organic phase was washed with sat. $NaHCO_3$ (aq., 150 mL), H_2O (2 x 150 mL), and dried with Na_2SO_4. Concentration and chromatography (hexanes:ethyl acetate, 15:1) gave **1.92** (12.2 g, 92%) as a white solid.

To a solution of **1.92** (8.80 g, 27.3 mmol), imidazole (4.19 g, 54.6 mmol) and DMF (150 mL) at rt was added TBDPSCl (9.76 g, 35.5 mmol) over 0.5 h. After stirring for 12 h, the reaction was quenched with water (100 mL). The phases were separated and the aqueous phase was extracted with ether (3 x 200 mL). The organic extracts were washed with brine (100 mL) and then concentration. Chromatography (hexanes:ethyl acetate, 50:1) provided **1.93** (15.3 g, 95%)as a colorless oil.

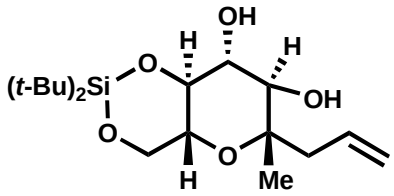
To slurry of **1.93** (13.5 g, 25.8 mmol) in THF (3.40 mL) at 0 °C was added *t*BuLi (0.121 L of a 1.70 M solution in pentane, 0.206 mol). After stirring for 0.5 h the reaction was cooled to –70 °C and diluted with THF (62 mL); CH_3I (32.1 mL, 0.515 mmol) was added over 0.5 h. After warming to rt the reaction was quenched with sat. NH_4Cl (aq.,1 L). The aqueous phase was extracted with ether (3 x 1 L). The extracts were dried with Na_2SO_4. Concentration and chromatography (hexanes:ethyl acetate, 50:1) provided **1.94** (13.6 g, 98%) as a white solid. R_f 0.67 (hexanes:ethyl acetate, 10:1); $[\alpha]_D^{20}$ = -17.9 (*c* = 0.50, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.96 (dd, *J* = 7.8, 1.5 Hz, 2 H), 7.91-7.89 (m, 2 H), 7.28-7.15 (m, 6 H), 4.56 (m, 1 H), 4.42 (brs, 1 H), 4.31 (dd, *J* = 10.7, 7.3 Hz, 1 H), 4.12 (dd, *J* = 10.3, 5.4 Hz, 1 H), 3.97 (t, *J* = 10.3 Hz, 1H), 3.65 (ddd, *J* = 10.3, 10.3, 5.7 Hz, 1 H), 1.46 (s, 3 H), 1.27 (s, 9 H), 1.10 (s, 9 H), 1.02 (s, 9 H); ^{13}C NMR (125 MHz, C_6D_6) δ 151.0, 136.6, 136.3, 135.2, 129.9, 129.9, 128.6, 100.8, 77.9, 72.9, 72.8, 66.4, 27.7, 27.2, 22.9, 20.0, 19.7, 19.0; IR (neat) 2932, 2858, 1679, 1472 cm^{-1}.



1. 95

(4aR,6S,7R,8R,8aR)-6-allyl-2,2-di-tert-butyl-8-(tert-butyldiphenylsilyloxy)-6-methyl-hexahydropyrano[3,2-d][1,3,2]dioxasilin-7-ol (1.95). To a solution of **1.94** (2.74 g, 5.09 mmol) and CH_2Cl_2 (83.0 mL) at –78 °C was added a solution of dimethyl dioxirane (31.9 mL of a 0.18 M solution in CH_2Cl_2, 5.74 mmol) dropwise. The reaction was warmed to 0 °C. After stirring at 0 °C for 0.5 h, the reaction was cooled to -78 °C and a solution of allyl magnesium chloride (25 mL of a 2.0 M solution in THF, 50 mmol) was added. After stirring for an additional 0.2 h at -78 °C, the reaction mixture was quenched

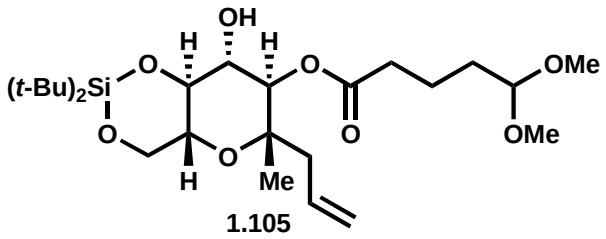
with sat. NH_4Cl (aq., 200 mL) and allowed to warm to rt. The aqueous phase was extracted with CH_2Cl_2 (5 x 100 mL) and dried with Na_2SO_4. Concentration and chromatography (hexanes:ethyl acetate, 50:1 to 20:1) provided **1.95** (2.79 g, 92%) as a colorless oil. R_f 0.55 (hexanes:ethyl acetate, 10:1); $[\alpha]_D^{20}$ = -4.68 (*c* = 0.39, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.95 (dd, *J* = 8.3, 1.8 2 H), 7.84-7.80 (m, 2 H), 7.25-7.15 (m, 6 H), 6.01-5.93 (dddd, *J* = 17.6, 10.3, 7.3, 7.3 Hz 1 H), 5.05-4.98 (m, 2 H), 4.17-4.14 (dd, *J* = 10.3, 4.9 Hz 1 H), 4.01-3.95 (m, 2 H), 3.91 (t, *J* = 9.8 Hz, 1 H) 3.60-3.53 (m, 2 H), 2.36-2.26 (m, 2 H), 1.25 (s, 9 H), 1.15 (s, 9 H), 1.06 (s, 9 H), 1.00 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 137.3, 136.9, 135.7, 134.0, 130.2, 130.0, 128.3, 117.9, 79.3, 78.2, 77.8, 76.4, 69.1, 67.8, 45.1, 27.8, 27.4, 27.3, 22.9, 20.1, 20.0, 16.5; IR (neat) 3577, 2934, 2859, 1473 cm^{-1}.



1. 96

(4aR,6S,7R,8R,8aS)-6-allyl-2,2-di-tert-butyl-6-methyl-hexahydropyrano[3,2-d][1,3,2]dioxasiline-7,8-diol (1.96). To a solution of **1.95** (2.40 g, 4.03 mmol) and HMPA (60 mL) was added NaH (0.435 g, 18.1mmol) at 0 ^oC. After stirring at 0 ^oC for 3 h, the reaction was quenched with sat. NH_4Cl (aq., 300 mL) and then the aqueous phase was extracted with ether (5 x 100 mL). The extracts were washed with brine (200 mL) and dried with Na_2SO_4. Concentration and chromatography (hexanes:ethyl acetate, 10:1 to 5:1) provided diol **1.96** (1.24 g, 86%) as a colorless oil. R_f 0.68 (hexanes:ethyl acetate, 1:1); $[\alpha]_D^{20}$ = -4.47 (*c* = 0.29, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 6.10-6.01 (dddd, *J* =

17.6, 10.3, 7.3, 7.3 Hz, 1 H), 5.13-5.09 (m, 2 H), 4.18-4.15 (dd, *J* = 10.3, 4.9 Hz, 1 H), 3.88 (t, *J* = 10.3 Hz, 1 H) 3.72-3.62 (m, 3 H), 3.53 (d, *J* = 9.3 Hz, 1 H), 3.13 (brs, 2 H) 2.52-2.41 (m, 2 H), 1.23 (s, 3 H), 1.08 (s, 18 H); ^{13}C NMR (125 MHz, C_6D_6) δ 135.3, 118.0, 78.8, 77.9, 75.6, 75.2, 68.7, 67.7, 45.1, 27.7, 27.3, 26.8, 22.8, 20.1, 16.9; IR (neat) 3419, 2935, 2860, 1098 cm^{-1}.

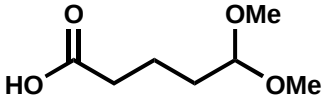


1.105

(4aR,6S,7R,8R,8aS)-6-allyl-2,2-di-tert-butyl-8-hydroxy-6-methyl-hexahydro-pyrano[3,2-d][1,3,2]dioxasilin-7-yl 5,5-dimethoxypentanoate (1.105). To a solution of **1.96** (0.925 g, 2.58 mmol), *i*-Pr_2NEt (1.16 ml, 6.60 mmol) and CH_2Cl_2 (116 mL) at -78 ^oC was added TMSOTf (0.470 ml, 2.58 mmol). After stirring at -78 ^oC for 1 h, the reaction was quenched with sat. $NaHCO_3$ (aq., 100 mL) and then the reaction mixture was extracted with CH_2Cl_2 (5 x 60 mL). The organic extracts were washed with brine (100 mL) and dried with Na_2SO_4. Concentration and chromatography (hexanes:ethyl acetate, 25:1) provided **1.97** (0.90 g, 81%) as a colorless oil.

To a solution of **1.97** (1.40 g, 3.26 mmol) in CH_2Cl_2 (23 mL) at rt was added acid **1.103** (0.814 g, 5.02 mmol, prepared according to the procedure given below), followed by 1,3-dicyclohexylcarbodiimide (2.08 g, 10.1 mmol) and DMAP (0.821 g, 6.71 mmol). After stirring at rt for 12 h, the reaction mixture was filtered. The filtrate was washed with sat. $NaHCO_3$ (aq., 25 mL), extracted with CH_2Cl_2 (5 x 25 mL), and dried with Na_2SO_4. Concentration and chromatography (hexanes:ethyl acetate, 50:1 to 25:1) provided **1.104** (1.54 g, 82%) as a colorless oil.

To a solution of **1.104** (1.50 g, 2.61 mmol) and MeOH (75mL) at rt was added H_2O (7.5 mL) and AcOH (4.48 mL, 78.3 mmol). After stirring at rt for 1 h, the reaction was quenched with sat. $NaHCO_3$ (aq., 60mL), extracted with CH_2Cl_2 (5 x 40 mL), and dried with Na_2SO_4. Concentration and chromatography (hexanes:ethyl acetate, 10:1 to 5:1) provided **1.105** (1.24, 95%) as a colorless oil. R_f 0.35(hexanes:ethyl acetate, 5:1); $[\alpha]_D^{20}$ = -8.0 (*c* = 0.51, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 5.99-5.91 (m, 1H), 5.19 (d, *J* = 9.3 Hz, 1 H), 5.11-5.08 (m, 2 H), 4.25 (t, *J* = 5.4 Hz, 1 H), 4.11 (dd, *J* = 9.8, 4.9 Hz, 1H), 3.82 (t, *J* = 9.8 Hz, 1 H), 3.76 (t, *J* = 9.3 Hz, 1 H), 3.69 (t, *J* = 9.3 Hz, 1 H), 3.61-3.57 (m, 1 H), 3.11 (s, 6 H), 2.79 (s, 1 H), 2.33-2.17 (m, 4 H), 1.74-1.68 (m, 2 H), 1.66-1.61 (m, 2 H), 1.15 (s, 3 H), 1.05 (s, 9 H), 1.04 (s, 9 H); ^{13}C NMR (125 MHz, C_6D_6) δ172.2, 132.8, 118.7, 104.3, 79.0, 77.1, 75.2, 73.7, 68.7, 67.5, 52.4, 52.3, 45.1, 34.2, 31.9, 27.7, 27.3,22.8, 20.5, 20.1, 17.5; IR (neat) 3360, 2939, 1749, 1098 cm^{-1}; LRMS (CI) calcd for $C_{25}H_{47}O_8Si$ 503.3 (MH^+), found 503.3.



1. 103

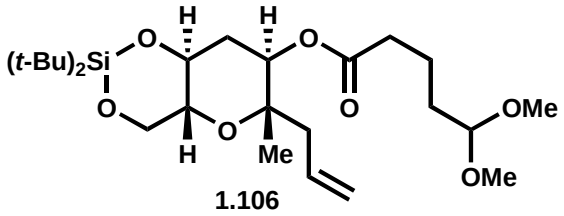
5,5-dimethoxypentanoic acid (1.103). A solution of δ-valerolactone (5.0 g, 50mmol) and concentrated H_2SO_4 (ca. 0.025 mL) in dry methanol (50 ml) was heated under reflux for 3 d. The mixture was cooled in an ice bath and $NaHCO_3$ (0.5 g) was added. After stirring for 10 min, the solid was separated by filtration. Concentration afforded a mixture of **1.100** (90%) and δ-valerolactone (10%).

The crude product from above was dissolved in dry CH_2Cl_2 (50 ml) and then the solution was added to a solution of PCC (12g, 0.056 mmol) in CH_2Cl_2 (20 ml). After stirring at rt for 2 h, the mixture was diluted with pentane (100 ml). The solid was filtered.

Concentration afforded aldehyde **1.101** which was converted into the corresponding acetal without further purification.

To the solution of **1.101** in CH_2Cl_2 (15 ml) at 0 ^oC was added a solution of 25ml methanol and 0.25 mL concentrated H_2SO_4. Trimethyl orthoformate (5.15 ml, 47.1 mmol) was added. After stirring at 0 ^oC for 2 h, the reaction was quenched with sat. $NaHCO_3$ (aq., 20 mL), extracted with CH_2Cl_2 (5 x 100 mL), and dried with Na_2SO_4. Concentration and chromatography (hexanes:ethyl acetate, 10:1 to 5:1) afforded acetal **1.102** (4.43 g, 50.4% from δ-valerolactone).

The acetal **1.102** (4.0 g, 27mmol) was dissolved in a solution of 1 N NaOH (30 mL, 30 mmol) and methanol (30 mL). After stirring for 2 h, the reaction was washed with ether (3 x 50 mL) and the aqueous was neutralized to pH = 3 by addition of 1 N HCl. The mixture was extracted with CH_2Cl_2 (5 x 100 mL) and then dried with Na_2SO_4. Concentration afforded the acid **1.103** (3.39 g, 92%) as a colorless oil whose spectrum matched that published previously.[44]

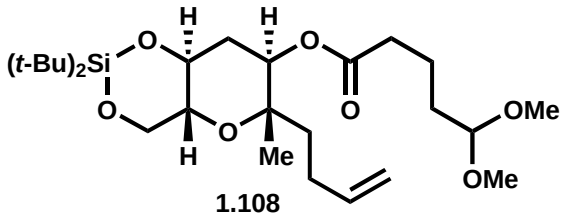


1.106

(4aR,6S,7R,8aS)-6-allyl-2,2-di-tert-butyl-6-methyl-hexahydropyrano[3,2-d]--[1,3,2] dioxasilin-7-yl 5,5-dimethoxypentanoate (1.106). To **1.105** (0.913 g, 1.82 mmol) in CS_2 (30.0 mL, 499 mmol) at -25 ^oC was added NaH (0.248 g, 10.3 mmol).After the reaction mixture was allowed to warm to -5 ^oC over 1 h, MeI (5.66 mL, 90.9 mmol) was added dropwise, and the reaction was warmed to 15 ^oC over 2 h. The reaction mixture was quenched with sat. NH_4Cl (aq., 60 mL), extracted with CH_2Cl_2 (5 x 40 mL), and

dried with Na_2SO_4. The solution was concentrated and the crude xanthate was taken on to the subsequent deoxygenation reaction without further purification.

To a solution of the xanthate ester (1.07 g, 1.82 mmol) from above and benzene (15 mL) at rt was added tributyltin hydride (7.40 mL, 27.4 mmol). The reaction mixture was heated to reflux and then AIBN (ca. 10 mg) was added. After 1 h, the reaction mixture was cooled to rt. Concentration and chromatography (hexanes:ethyl acetate, 10:1) provided **1.106** (0.708 g, 80% over two steps) as a colorless oil. R_f 0.55 (hexanes:ethyl acetate, 3:1); $[\alpha]_D^{20}$ = -11.3 (*c* = 0.61, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 5.94 (dddd, *J* = 18.0, 10.5, 7.5 Hz, 1 H), 5.04 (m, 2 H), 4.99 (dd, *J* = 12.0, 4.5 Hz, 1 H), 4.21 (t, *J* = 5.8 Hz, 1 H), 4.12 (dd, *J* = 9.8, 4.8 Hz, 1 H), 3.82 (t, *J* = 10.0 Hz, 1 H), 3.78 (ddd, *J* = 11.8, 9.8, 4.8 Hz, 1 H), 3.57 (ddd, *J* = 9.8, 5.0 Hz, 1 H), 3.10 (s, 3 H), 3.09 (s, 3 H), 2.29-2.20 (m, 2 H), 2.07 (t, *J* = 7.0 Hz, 2 H), 1.71-1.61 (m, 3 H), 1.58-1.53 (m, 3 H), 1.17 (s, 3 H), 1.07 (s, 9 H), 1.03 (s, 9 H); ^{13}C NMR (125 MHz, C_6D_6) δ 172.0, 133.8, 118.6, 104.6, 76.3, 73.6, 72.0, 71.2, 68.3, 52.7, 52.7, 45.3, 35.1, 34.4, 32.4, 28.0, 27.7, 23.1, 20.8, 20.5, 16.8; IR (neat) 2939, 1742, 1470, 1096 cm^{-1}; LRMS (CI) calcd for $C_{25}H_{47}O_7Si$ 487.3 (MH^+), found 487.4.



1.108

(4aR,6S,7R,8aS)-6-(but-3-enyl)-2,2-di-tert-butyl-6-methyl-hexahydropyrano [3,2-d][1,3,2]dioxasilin-7-yl 5,5-dimethoxypentanoate (1.108). To **1.106** (0.625 g, 1.29 mmol) in THF (40 mL) at 0 °C was added BH_3·DMS (0.80ml of a 10.0 M solution in DMS, 8.0 mmol) dropwise. After stirring at 0 °C for 2 h, the reaction was quenched with

the addition of sat. $NaHCO_3$ (aq., 38 mL) dropwise, followed by the addition of aq. H_2O_2 (5.16 mL of a 30% solution) dropwise. After stirring at 0 °C for 0.5 h, sat. $Na_2S_2O_3$ (aq., 100 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (5 x 50 mL) then dried with Na_2SO_4. Concentration and chromatography (hexanes:ethyl acetate, 10:1 to 3:1) provided the primary alcohol **1.107** (0.507 g, 78%) as a colorless oil.

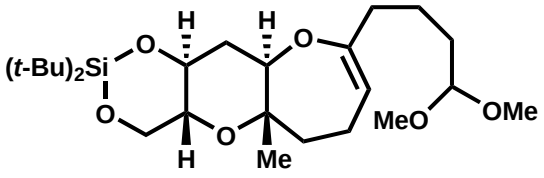
To the solution of **1.107** (0.31 g, 0.62 mmol) in CH_2Cl_2 (10 ml) at rt was added 4Å MS (0.40 g), NMO (0.155 g, 1.54 mmol), and TPAP (ca. 5 mg). After stirring at rt for 1h, the reaction mixture was filtered through neutralized silica. The solution was concentrated and the crude aldehyde was taken on to the subsequent Wittig reaction without further purification.

To the crude aldehyde (0.35 g) from above was added THF (72 mL) at rt. Then Wittig reagent (6.2 mL of a 0.15 M solution, 0.93 mmol, prepared according to the procedure below) was added dropwise. After stirring at rt for 0.3 h, the reaction was quenched with sat. NH_4Cl (aq., 30 mL), extracted with CH_2Cl_2 (5 x 20 mL) and dried with Na_2SO_4. Concentration and chromatography (hexanes:ethyl acetate, 50:1) provided **1.108** (0.25 g, 80% over two steps) as a colorless oil.

The methylene Wittig reagent was prepared as follows: To methyltriphenyl phosphonium bromide (0.175 g, 0.490 mmol) in THF (2.5 mL) was added a solution of potassium *tert*-butoxide (0.45 mL of a 1.0 M solution in THF, 0.45 mmol) dropwise at rt. The resulting yellow solution was used after stirring for 0.3 h.

Data for **1.108**: R_f 0.60 (hexanes:ethyl acetate, 3:1); $[\alpha]_D^{20}$ = -17.3 (*c* = 0.35, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 5.78 (dddd, *J* = 16.8, 10.3, 6.8 Hz, 1 H), 5.07-5.01 (m, 2 H), 4.94 (dd, *J* = 10.5, 2.0 Hz, 1 H), 4.21 (t, *J* = 5.5 Hz, 1 H), 4.13 (dd, *J* = 10.0, 5.0

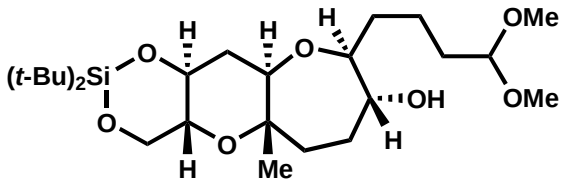
Hz, 1 H), 3.83 (t, *J* = 10.0 Hz, 1 H), 3.80 (partially overlapping ddd, *J* = 11.3, 9.3, 4.3 Hz, 1 H), 3.59 (ddd, *J* = 9.8, 4.8 Hz, 1 H), 3.10 (s, 3 H), 3.09 (s, 3 H), 2.46 (dt, *J* = 8.5, 4.0 Hz, 1 H), 2.36-2.30 (m, 1 H), 2.20-2.12 (m, 1 H), 2.05 (t, *J* = 7.5 Hz, 2 H), 1.74 (m, 1 H), 1.69-1.61 (m, 3 H), 1.60-1.53 (m, 3 H), 1.16 (s, 3 H), 1.11 (s, 9 H), 1.07 (s, 9 H); ^{13}C NMR (125 MHz, C_6D_6) δ 172.2, 139.4, 115.0, 104.6, 76.0, 73.7, 72.2, 71.2, 68.3, 52.7, 52.6, 40.0, 35.1, 34.4, 32.4, 28.0, 27.7, 23.1, 20.8, 20.5, 16.8; IR (neat) 2939, 2862, 1741, 1095 cm^{-1}; LRMS (CI) calcd for $C_{26}H_{49}O_7Si$ 501.3 (MH^+), found 501.4.



1.109

Seven-membered cyclic enol ether ring (1.109). To a solution of $TiCl_4$ (0.65 mL, 5.9 mmol) in CH_2Cl_2 (54 mL) at 0 °C was added THF (2.87mL, 35.8 mmol) dropwise. The solution was stirred at 0 °C for 0.2 h and then TMEDA (5.32 mL, 35.7 mmol) was added dropwise to the resulting light-yellow solution. The ice bath was removed and after 0.3 h Zn dust (0.868 g, 13.4 mmol) was added followed by $PbCl_2$ (0.196 g, 0.705 mmol). Over 0.3 h, the reaction slurry turned from green to blue to blue-green at which time a solution of **1.108** (0.10 g, 0.20 mmol), CH_2Br_2 (0.416 ml, 5.93 mmol), and CH_2Cl_2 (12 mL) was added via a cannula. The resulting mixture was stirred rapidly and heated at reflux for 1.6 h. Then the reaction mixture was cooled to 0 °C and stirred with sat. K_2CO_3 (aq., 1.33 mL) for 0.5 h. The mixture was filtered through a plug of neutral silica and concentrated. Flash chromatography (hexanes:ethyl acetate, 100:1 w/ 2% Et_3N) provided crude acyclic enol ether as a colorless oil that was taken on to the ring closing metathesis reaction.

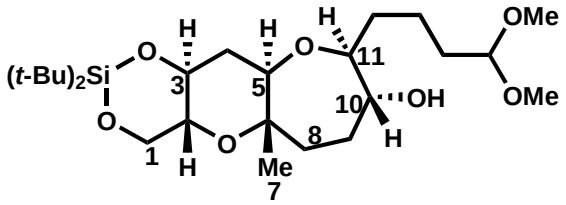
To the crude acyclic enol ether (100 mg) in hexane (15 ml) in a glove box at rt was added Schrock's molybdenum catalyst (30.4 mg, 0.040 mmol). The reaction was sealed, removed from the glove box and then heated at 60 °C for 16 h. Concentration and chromatography (hexanes:ethyl acetate, 100:1 w/ 2% Et_3N) provided the cyclic enol ether **1.109** (51.7 mg, 55% over two steps) as a colorless oil. R_f 0.70 (hexanes:ethyl acetate, 3:1); $[\alpha]_D^{20}$ = +17.4 (*c* = 0.25, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 4.60 (dd, *J* = 3.3 Hz, 1 H), 4.32 (t, *J* = 5.3 Hz, 1 H), 4.20 (dd, *J* = 10.0, 5.0 Hz, 1 H), 3.88 (t, *J* = 9.8 Hz, 1 H), 3.78 (ddd, *J* = 11.3, 9.5, 5.0 Hz, 1 H), 3.68 (ddd, *J* = 9.5, 4.8 Hz, 1 H), 3.41 (dd, *J* = 12.3, 4.3 Hz, 1 H), 3.15 (s, 3 H), 3.14 (s, 3 H), 2.44 (dt, *J* = 12.0, 4.8 Hz, 1 H), 2.10-2.03 (m, 1 H), 2.00-1.89 (m, 2 H), 1.88-1.80 (m, 1 H), 1.76 (dt, *J* = 14.5, 4.0, 1 H), 1.69-1.58 (m, 3 H), 1.50 (ddd, *J* = 12.8, 3.8 Hz, 1 H), 1.22 (s, 3 H), 1.10 (s, 9 H), 1.09 (s, 9 H); ^{13}C NMR (125 MHz, C_6D_6) δ 160.0, 128.9, 105.7, 104.9, 82.0, 78.4, 74.4, 70.9, 68.5, 52.7, 52.5, 41.1, 36.8, 36.5, 32.7, 28.1, 27.7, 23.2, 23.0, 21.6, 20.5, 14.6; IR (neat) 2952, 2889, 1464, 1073 cm^{-1}; LRMS (CI) calcd for $C_{25}H_{47}O_6Si$ 471.3 (MH^+), found 471.4.



1.112

Preparation of alcohol 1.112. To **1.109** (70.0 mg, 0.149 mmol) in CH_2Cl_2 (26.0 mL) at –78 °C was added dimethyl dioxirane (2.8 mL of a 0.10 M solution in CH_2Cl_2, 0.28 mmol) dropwise. The reaction was warmed to 0 °C and concentrated. The colorless oil was taken up in CH_2Cl_2 (38 mL), cooled to -78 °C and *i*Bu_2AlH (0.28 mL of a 1.0 M solution in hexanes, 0.28 mmol) was added at once. After stirring at -78 °C for 0.3 h, the reaction was quenched with sat. NH_4Cl (aq., 25 mL), extracted with CH_2Cl_2 (5 x 20 mL)

and dried with Na_2SO_4. Concentration and chromatography (hexanes:ethyl acetate, 20:1 to 5:1) provided **1.112** (51.0 mg, 78% over two steps) as a colorless oil. $[\alpha]_D^{20}$ = +27.6 (*c* = 0.13, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 4.33 (t, *J* = 5.5 Hz, 1 H), 4.25 (dd, *J* = 10.3, 4.8 Hz, 1 H), 3.92 (t, *J* = 10.0 Hz, 1 H), 3.77 (ddd, *J* = 11.0, 9.3, 4.5 Hz, 1 H), 3.69 (ddd, *J* = 10.0, 5.0 Hz, 1 H), 3.62 (dd, *J* = 12.0, 4.5 Hz, 1 H), 3.41 (ddd, *J* = 11.5, 5.0, 2.0 Hz, 1 H), 3.37-3.32 (m, 1 H), 3.16 (s, 3 H), 3.15 (s, 3 H), 2.23 (dt, *J* = 12.0, 4.5 Hz, 1 H), 2.11 (ddd, *J* = 12.5, 3.0 Hz, 1 H), 1.78 (q, *J* = 23.3, 11.8 Hz, 1 H), 1.72-1.55 (m, 3 H), 1.54-1.44 (m, 3 H), 1.43-1.29 (m, 3 H), 1.25 (s, 3 H), 1.11 (s, 9 H), 1.09 (s, 9 H); ^{13}C NMR (125 MHz, C_6D_6) δ 105.0, 85.7, 77.8, 77.7, 75.2, 74.6, 70.9, 68.7, 52.7, 52.6, 37.1, 35.5, 35.2, 33.1, 28.1, 27.8, 27.2, 21.8, 20.5, 16.4; IR (neat) 3351, 2361, 1469, 1090 cm^{-1}; LRMS (CI) calcd for $C_{25}H_{49}O_7Si$ 489.3 (MH^+), found 489.3.



Summary of COSY spectrum for **1.112**:

Proton at 4.25 ppm (H-1) shows crosspeaks with protons at 3.92 ppm (H-1) and 3.69 ppm (H-2)

Proton at 3.92 ppm (H-1) shows crosspeaks with protons at 4.25 ppm (H-1) and 3.69 ppm (H-2)

Proton at 3.69 ppm (H-2) shows crosspeaks with protons at 3.77 ppm (H-3), 4.25 ppm (H-1) and 3.92 ppm (H-1)

Proton at 3.77 ppm (H-3) shows crosspeaks with protons at 3.69 ppm (H-2), 2.23 ppm (H-4) and 1.78 ppm (H-4)

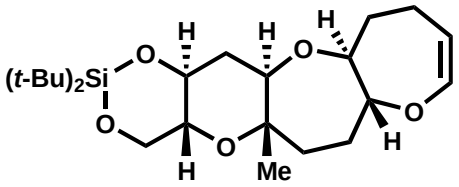
Proton at 3.62 ppm (H-5) shows crosspeaks with protons at 2.23 ppm (H-4) and 1.78 ppm (H-4)

Summary of 1D nOe difference experiments for **1.112**:

Irradiation at 1.25 ppm (CH_3-7) resulted in enhancement at 3.69 ppm (H-2) and 3.35 ppm (H-10)

Irradiation at 3.62 ppm (H-5) resulted in enhancement at 3.77 ppm (H-3) and 3.40 ppm (H-11)

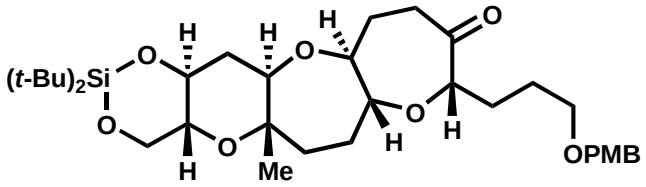
Irradiation at 3.40 ppm (H-11) resulted in enhancement at 3.62 ppm (H-5)



1.113

Preparation of cyclic enol ether 1.113. To **1.112** (51.0 mg, 0.104 mmol) in chlorobenzene (9.60 mL) at rt was added pyridine (0.05 mL, 0.625 mmol), followed by PPTS (0.381 mg, 1.52 mmol). The reaction mixture was heated to 140 °C for 3 h. At this time, the mixture was cooled to rt and quenched with sat. $NaHCO_3$ (aq., 20 mL), extracted with CH_2Cl_2 (5 x 20 mL), and dried with Na_2SO_4. Concentration and chromatography (hexanes:ethyl acetate, 50:1 to 10:1) provided **1.113** (44.3 mg, 80%) as a colorless oil. R_f 0.49 (hexanes:ethyl acetate, 10:1); $[\alpha]_D^{20}$ = +7.6 (*c* = 0.11, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 6.33 (d, *J* = 6.5 Hz, 1 H), 4.54 (ddd, *J* = 6.5, 3.8 Hz, 1 H), 4.18 (dd, *J* = 10.0, 4.5 Hz, 1 H), 4.00 (q, *J* = 16.0, 7.5 Hz, 1 H), 3.88 (t, *J* = 10.0 Hz, 1 H), 3.76 (ddd, *J* = 11.0, 9.3, 4.5 Hz, 1 H), 3.62 (ddd, *J* = 9.5, 4.3 Hz, 1 H), 3.47 (ddd, *J* = 9.0, 4.5 Hz, 1 H), 2.99 (dd, *J* = 12.0, 4.5 Hz, 1 H), 2.45-2.36 (m, 1 H), 2.23-2.11 (m, 2 H), 2.00-1.92 (m, 1 H), 1.85-1.70 (m, 4 H), 1.68-1.60 (m, 1 H), 1.13 (s, 9 H), 1.09 (s, 9 H), 1.08 (s,

3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 148.4, 113.7, 84.6, 83.7, 83.5, 77.7, 77.6, 74.9, 70.9, 69.0, 37.6, 36.8, 34.6, 29.2, 28.1, 27.7, 23.2, 21.4, 20.5, 16.0; IR (neat) 2931, 2859, 1091 cm^{-1}; LRMS (CI) calcd for $C_{23}H_{41}O_5Si$ 425.3 (MH^+), found 425.3.



1.119

Preparation of ketone 1.119. To **1.113** (30.0 mg, 0.0706 mmol) in CH_2Cl_2 (9.0 mL) at -78 °C was added dimethyl dioxirane (1.4 mL of a 0.10 M solution in CH_2Cl_2, 0.14 mmol) dropwise. The reaction mixture was warmed to 0 °C and concentrated. The colorless oil was taken up in CH_2Cl_2 (11.4 mL), cooled to -78 °C, and allyl magnesium chloride (0.18 mL of a 2.0 M solution in THF, 0.35 mmol) was added at once. After stirring at -78 °C for an additional 0.2 h, the reaction mixture was warmed to rt and quenched with sat. NH_4Cl (aq., 20 mL). The phases were separated. The aqueous phase was extracted with CH_2Cl_2 (5 x 20 mL) and dried with Na_2SO_4.Concentration and chromatography (hexanes:ethyl acetate, 20:1 to 5:1) provided alcohol **1.114** and **1.115** as a 2:1 mixture (26.5 mg, 78%).

To the mixture above (26.5 mg, 0.0550 mmol) in CH_2Cl_2 (1.6 mL) at rt was added *i*-Pr_2NEt (0.166 ml, 0.956 mmol), Ac_2O (0.083 mL, 0.88 mmol) and then DMAP (ca. 5mg). After stirring at rt for 1 h, the reaction was diluted with CH_2Cl_2(10 mL) and quenched with sat. $NaHCO_3$ (aq., 4 mL). The phases were separated. The aqueous phase was extracted with CH_2Cl_2 (5 x 10 mL) and dried with Na_2SO_4. Concentration and chromatography (hexanes:ethyl acetate, 20:1) provided the acetates corresponding to **1.114** and **1.115** as colorless oils (27.4 mg, 95%).

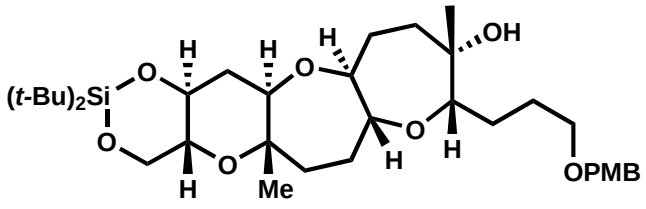
To the acetates (27.4 mg, 0.0520 mmol) in THF (1.6 mL) at 0 ^{o}C was added BH_3·DMS (0.040mL of a 1.0 M solution in DMS, 0.40 mmol) dropwise. After stirring at 0 ^{o}C for 2 h, the reaction was quenched with the addition of sat. $NaHCO_3$ (aq., 3 mL) dropwise, followed by addition of aq. H_2O_2 (0.3 mL of a 30% solution) dropwise. After stirring at 0 ^{o}C for 0.5 h, sat. $Na_2S_2O_3$ (aq., 9 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (5 x 10 mL).The extracts were dried with Na_2SO_4, concentrated and taken on to the protection without further purification.

To the crude alcohol from above in Et_2O (1.0 mL) at 0 ^{o}C was added 4-methoxybenzyl acetimidate (0.033 mL, 0.13 mmol) followed by TfOH (ca. 0.125 ml of a 2 x10 $^{-3}$ M solution). The reaction mixture was warmed to rt over 1 h then quenched with sat. $NaHCO_3$ (aq., 3 mL), extracted with CH_2Cl_2 (5 x 10 mL) and dried with Na_2SO_4. Concentration and chromatography (hexanes:ethyl acetate, 50:1 to 20:1) provided the corresponding PMB ethers as colorless oil (18.9 mg, 55% over two steps).

The PMB ethers (18.9 mg, 0.0285 mmol) were taken up in MeOH (3.0 mL) and potassium carbonate (30.0 mg, 0.217 mmol) was added at once. After stirring at rt for 1 h, the reaction was diluted with H_2O (3.0 mL), extracted with CH_2Cl_2 (5 x 10 mL) and dried with Na_2SO_4. Concentration and chromatography (hexanes:ethyl acetate, 20:1 to 5:1) provided the corresponding secondary alcohols as colorless oils (16.8 mg, 95%).

To the alcohols (16.8 mg, 0.0272 mmol) from above in CH_2Cl_2 (3.0 mL) at rt was added 4Å MS (50.0 mg), NMO (15.0 mg, 0.148 mmol), then TPAP (ca. 2 mg). After stirring at rt for 1 h, the reaction mixture was filtered through neutralized silica plug. Concentration and chromatography (hexanes:ethyl acetate, 50:1 to 10:1) provided ketone **1.119** (10 mg, 57%) and **1.120** (5 mg, 28%) as colorless oils.

To the minor isomer **1.120** (5.0 mg, 0.0081 mmol) in toluene (2.0 mL) was added imidazole (18.0 mg, 0.264 mmol). After refluxing overnight, the reaction was cooled to rt and concentrated. Chromatography (hexanes:ethyl acetate, 50:1 to 10:1) provided **1.119** (4.3 mg, 85%) as a colorless oil. R_f 0.56 (hexanes:ethyl acetate, 3:1); $[\alpha]_D^{20}$ = +13.4 (*c* = 0.11, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.21 (d, *J* = 8.5 Hz, 2 H), 6.79 (d, *J* = 8.5 Hz, 2 H), 4.30 (d, *J* = 3.5 Hz, 2 H), 4.21 (dd, *J* = 10.3, 4.9 Hz, 1 H), 3.90 (t, *J* = 10.3 Hz, 1 H), 3.81(ddd, *J* = 11.0, 9.0, 4.4 Hz, 1 H), 3.67 (ddd, *J* = 9.8, 4.9 Hz, 1 H), 3.61 (dd, *J* = 8.8, 4.3 Hz, 1 H), 3.33-3.29 (m, 1 H), 3.29 (overlapping s, 3 H), 3.20 (dd, *J* = 12.2, 4.0 Hz, 1 H), 3.08 (ddd, *J* = 10.8, 3.9 Hz, 1 H), 2.66 (ddd, *J* = 9.0, 4.5, 1 H), 2.57-2.50 (m, 1 H), 2.21 (dt, *J* = 12.0, 4.3 Hz, 1 H), 2.14-2.10 (m, 1 H), 1.93-1.63 (m, 8 H), 1.51 (ddd, *J* = 14.3, 10.3, 3.5 Hz, 1 H), 1.35 (m, 1 H), 1.14 (s, 9 H), 1.14(s, 3 H), 1.10 (s, 9 H); ^{13}C NMR (125 MHz, C_6D_6) δ 214.7, 131.6, 129.8, 114.4, 87.2, 86.9, 85.0, 80.0, 77.7, 74.9, 73.2, 71.3, 70.0, 68.7, 55.1, 38.5, 37.2, 36.6, 31.9, 31.2, 30.2, 28.1, 27.7, 26.6, 23.2, 20.5, 18.4; IR (neat) 2937, 2862, 1715, 1084 cm^{-1}; LRMS (CI) calcd for $C_{34}H_{55}O_8Si$ 619.4 (MH^+), found 619.4.



1.122

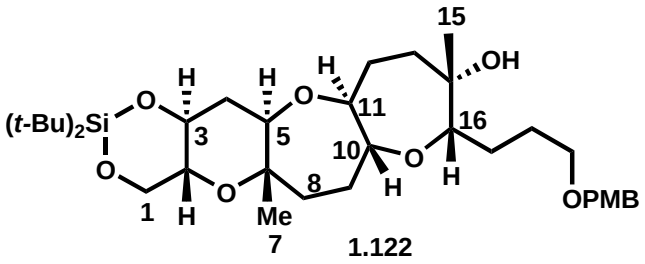
Preparation of alcohol 1.122. To the solution of **1.119** (12.0 mg, 0.019 mmol) in THF (1.6 mL) at rt was added the methylene Wittig reagent (0.50 mL of a 0.30 M solution, 0.15 mmol, prepared according to the procedure described in the experimental section for **1.108**). After stirring at rt for 1 h, the reaction was quenched with sat. NH_4Cl

(aq., 5 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (5 x 20 mL). The extracts were dried with Na_2SO_4. Concentration and chromatography (hexanes:ethyl acetate, 50:1 to 10:1) provided terminal olefin **1.121** (10.0 mg, 83%) as a colorless oil.

To a solution of **1.121** (10.0 mg, 0.0160 mmol) in toluene (2.0 mL) at 0 ^oC was added $NaHCO_3$ (66.0 mg, 0.785 mmol) followed by *m*CPBA (100 mg, 0.580 mmol). After stirring at 0 ^oC for 2 h, the reaction was quenched with $Na_2S_2O_3$ (aq., 10 mL).The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (5 x 20 mL). The extracts were dried with Na_2SO_4. Concentration and chromatography (hexanes:ethyl acetate, 50:1 to 5:1) provided the epoxide as a colorless oil.

To a solution of the epoxide (7.0 mg, 0.011 mmol) from above in THF (3.0 mL) at 0 ^oC was added $LiEt_3BH$ (0.050 mL of a 1.0 M solution in THF, 0.050 mmol). After stirring at 0 ^oC for 3 h, the reaction was quenched with H_2O (2 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (5 x 10 mL). The extracts were dried with Na_2SO_4. Concentration and chromatography (hexanes:ethyl acetate, 10:1 to 1:1) provided desired alcohol **1.122** (4.8 mg, 48% for three steps) and undesired alcohol **epi-1.122** (0.8 mg 8% for three steps) as colorless oils. R_f 0.60 (hexanes:ethyl acetate, 1:1); $[\alpha]_D^{20}$ = +51.2 (*c* = 0.073, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.26 (d, *J* = 8.5 Hz, 2 H), 6.81 (d, *J* = 8.5 Hz, 2 H), 4.36 (d, *J* = 7.0 Hz, 1 H), 4.21 (dd, *J* = 10.0, 5.0 Hz, 1 H), 3.90 (t, *J* = 10.0 Hz, 1 H), 3.80 (ddd, *J* = 11.3, 9.3, 4.8 Hz, 1 H), 3.64 (ddd, *J* = 10.0, 5.0 Hz, 1 H), 3.46-3.30 (m, 3 H), 3.31 (s, 3 H), 3.20-3.18 (m, 1 H), 3.15 (ddd, *J* = 8.8, 5.0 Hz, 1 H), 3.02 (dd, *J* = 12.0, 4.0 Hz, 1 H), 2.27 (dt, *J* = 12.5, 4.0 Hz, 1 H), 2.11-2.04 (m, 1 H), 1.99-1.88 (m, 2 H), 1.86-1.63 (m, 7 H), 1.58 (m, 2 H), 1.18 (s, 3 H), 1.14

(s, 3 H), 1.10 (s, 9 H), 1.00 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 129.8, 114.4, 88.7, 86.6, 85.5, 82.5, 77.9, 74.9, 74.5, 73.2, 71.0, 70.8, 68.7, 55.1, 38.9, 38.1, 36.9, 30.2, 29.8, 28.2, 28.1, 27.7, 24.0, 23.2, 20.5, 16.7; IR (neat) 3444, 2937, 2862, 1086 cm^{-1}; LRMS (CI) calcd for $C_{35}H_{59}O_8Si$ 635.4 (MH^+), found 635.4.



1.122

Summary of COSY spectrum for **1.122**:

Proton at 3.90 ppm (H-1) shows crosspeaks with protons at 4.21 ppm (H-1) and 3.64 ppm (H-2)

Proton at 4.21 ppm (H-1) shows crosspeaks with protons at 3.90 ppm (H-1) and 3.64 ppm (H-2)

Proton at 3.64 ppm (H-2) shows crosspeaks with protons at 3.80 ppm (H-3), 3.90 ppm (H-1) and 4.21 ppm (H-1)

Proton at 3.80 ppm (H-3) shows crosspeaks with protons at 3.64 ppm (H-2), 2.27 ppm (H-4) and 1.80 ppm (H-4)

Proton at 3.02 ppm (H-5) shows crosspeaks with protons at 2.27 ppm (H-4) and 1.80 ppm (H-4)

Summary of 1D nOe difference experiments for **1.122**:

Irradiation at 1.18 ppm (CH_3-7) resulted in enhancement at 3.64 ppm (H-2) and 3.33 ppm (H-10)

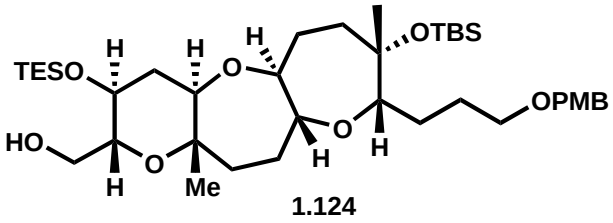
Irradiation at 3.64 ppm (H-2) resulted in enhancement at 1.18 ppm (CH_3-7) and 4.21 ppm (H-1)

Irradiation at 3.80 ppm (H-3) resulted in enhancement at 3.02 ppm (H-5) and 2.27 ppm (H-4)

Irradiation at 3.02 ppm (H-5) resulted in enhancement at 3.80 ppm (H-3) and 3.15 ppm (H-11)

Irradiation at 3.15 ppm (H-11) resulted in enhancement at 3.02 ppm (H-5)

Irradiation at 0.98 ppm (CH_3-15) resulted in enhancement at no other protons



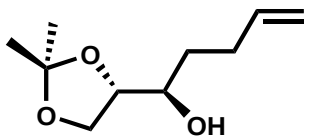
1.124

Preparation of alcohol 1.124. To the solution of **1.122** (4.0 mg, 6.3μmol) in CH_2Cl_2 (3.0 mL) at 0 ^oC was added NEt_3 (0.136 mL, 1.05 mmol) followed by TBSOTf (0.136 mL, 0.592 mmol) dropwise, and DMAP (ca. 0.5mg). The reaction was warmed to rt over 1 h at which time it was quenched with sat. $NaHCO_3$ (aq., 3 mL), extracted with CH_2Cl_2 (5 x 10 mL) and then dried with Na_2SO_4. Concentration and chromatography (hexanes:ethyl acetate, 50:1 to 10:1) provided protected alcohol **1.123 (**4.3 mg, 90%) as a colorless oil.

To the solution of **1.123 (**4.3 mg, 5.7μmol) in THF (2.0 ml) at rt was added HF·pyridine (0.04 mL of a 1.0 M solution in THF, 0.04 mmol). After stirring at rt for1 h, the reaction was quenched with sat. $NaHCO_3$ (aq., 3 mL), extracted with CH_2Cl_2 (5 x 10 mL) and then dried with Na_2SO_4. Concentration and chromatography (hexanes:ethyl acetate, 50:1 to 10:1) provided the diol as a colorless oil.

To the diol from above in CH_2Cl_2 (2.0 mL) at rt was added NEt_3 (0.16 mL, 1.2 mmol) followed by TESCl (0.080 mL, 0.47 mmol) and DMAP (ca. 0.5 mg). After stirring at rt for 1 h, the reaction was quenched with sat. $NaHCO_3$ (aq., 2.0 mL), extracted with CH_2Cl_2 (5 x 10 mL) and then dried with Na_2SO_4. The solution was concentrated and taken on to the next step without further purification.

To the crude diprotected alcohol in THF (1.2 mL) at 0 °C was added H_2O (0.6 mL) at once followed by AcOH (3.2 mL) dropwise. After stirring at 0 °C for 1 h, the reaction was quenched with sat. $NaHCO_3$ (aq., 3 mL), extracted with CH_2Cl_2 (5 x 10 mL) and dried with Na_2SO_4. Concentration and chromatography (hexanes:ethyl acetate, 10:1 to 3:1) provided alcohol **1.124** (2.0 mg, 50 % from **1.123**) as a colorless oil. R_f 0.47 (hexanes:ethyl acetate, 3:1); $[\alpha]_D^{20}$ = +1.67 (*c* = 0.36, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.27 (d, *J* = 9.5 Hz, 2 H), 6.83 (d, *J* = 8.5 Hz, 1 H), 4.37 (s, 2 H), 3.86-3.81 (m, 2 H), 3.80-3.62 (m, 2 H), 3.53-3.38 (m, 5 H), 3.31 (s, 3 H), 3.28-3.23 (m, 1 H), 3.03 (dd, *J* = 11.5, 4.0 Hz, 1 H), 2.26-2.18 (m, 1 H), 2.18-2.02 (m, 2 H), 2.0-1.93 (m, 1 H), 1.90-1.62 (m, 8 H), 1.56-1.46 (m, 2 H), 1.42-1.28 (m, 2 H), 1.13 (s, 3 H), 1.06 (s, 3 H), 0.98 (t, *J* = 7.8 Hz, 9 H), 0.95 (s, 9 H), 0.60 (q, *J* = 8.0 Hz, 6 H), 0.07 (3 H), 0.06 (3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 160.0, 129.7, 114.4, 89.3, 86.6, 84.9, 82.7, 78.0, 77.0, 75.2, 73.2, 71.0, 67.9, 63.1, 55.1, 38.3, 38.0, 37.5, 30.6, 30.0, 29.8, 28.2, 28.1, 26.7, 26.4, 24.3, 18.7, 16.1, 7.4, 5.7, -1.6, -1.7; IR (neat) 2950, 2931, 1461, 1086 cm^{-1}; LRMS (CI) calcd for $C_{39}H_{71}O_8Si_2$ 723.5 (MH^+), found 723.6.



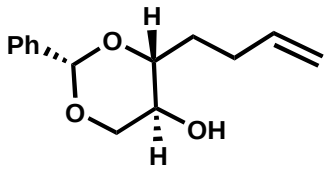
1.130

(R)-1-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-4-en-1-ol (1.130). A solution of L-gulono-1,4-lactone (4.44 g, 24.8 mmol) in DMF (40 mL) was cooled to 10 ^{o}C and *p*-toluenesulfonic acid (36 mg, 0.20 mmol) was added. To the resulting solution, isopropenyl methyl ether (3.1 mL, 32 mmol) was added dropwise at 10 ^{o}C. The reaction mixture was warmed to rt and stirred at rt over 24 h. The reaction was treated with $Na_2CO_3 \cdot 10H_2O$ (4.4 g) and stirred for 2 h. The reaction mixture was filtered. The filtrate was concentrated to give 5,6-O-isopropylidene-L-gulono-1,4-lactone which was used directly for the next step without further purification.

To a solution of sodium periodate (7.13 g, 33.3 mmol) and water (70 mL) at 0 ^{o}C was added NaOH (11 mL of a 3.0 M solution in H_2O, 33 mmol) dropwise at a rate such that the internal temperature was below 7 ^{o}C. 5,6-O-isopropylidene-L-gulono-1,4-lactone from above was added. After 0.5 h, the ice bath was removed. The reaction mixture was stirred at rt for 2 h at which time NaCl (8.5 g) was added. The reaction mixture was filtered and the white solide was washed with brine (2 x 10 mL). The filtrate was adjusted to pH = 7 with 15% Na_2CO_3 solution before extraction with CH_2Cl_2 (6 x 50 mL). The organic extracts were combined, dried with $MgSO_4$ and distillated to give 1,2-O-isopropylidene-(S)-glyceraldehyde**1.129** (1.0 g, 33% for two steps) as a colorless liquid.

To a solution of **1.129** (1.0 g, 7.7 mmol) in THF (10 mL) at -78 ^{o}C was added $ZnCl_2$ (32. mL of a 0.50 M solution in THF, 16. mmol).After stirring at -78 ^{o}C for 10 min, the reaction was cooled to -90 ^{o}C. Then a solution of homoallyl magnesium bromide (from 4-bromo-1-butene (1.62 mL, 16.0 mmol), Mg (0.77 g, 32. mmol) and THF (10 mL) was added. After stirring at -90 ^{o}C for 1 h, the reaction mixture was warmed to 0 ^{o}C and the reaction was quenched with sat. NH_4Cl (aq., 10 mL). The phases were separated. The

aqueous phase was extracted with CH_2Cl_2 (5 x 100 mL) and dried with Na_2SO_4. Concentration and chromatography (hexanes:ethyl acetate, 10:1 to 3:1) provided **1.130** (0.99 g, 70%) as a colorless oil. R_f 0.26 (hexanes:ethyl acetate, 2:1); $[\alpha]_D^{20}$ = -6.8 (*c* = 0.16, THF); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.80 (m, 1 H), 5.01 (m, 2 H), 4.03-3.85 (m, 3 H), 3.75 (m, 1 H), 2.34-2.08 (m, 2 H), 1.56-1.34 (m, 2 H), 1.40 (s, 3 H), 1.34 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.9, 115.3, 109.3, 79.4, 71.0, 65.7, 32.8, 30.5, 27.0, 25.8; IR (neat) 3438, 2935, 1216, 917 cm^{-1}; LRMS (APCI) calcd for $C_{10}H_{22}NO_3$ 204.2 ($M+NH_4^+$), found 203.9.

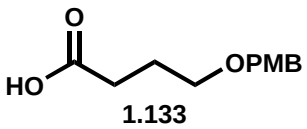


1.132

(4R,5S)-4-(but-3-enyl)-2-phenyl-1,3-dioxan-5-ol (1.132). To a solution of **1.130** (0.50 g, 2.7 mmol) in methanol (100 mL) at rt was added PPTS (0.74 g, 3.0 mmol). After refluxing overnight, the reaction was cooled to rt and quenched with sat. $NaHCO_3$ (aq., 10 mL). The phases were separated. The aqueous phase was extracted with CH_2Cl_2 (5 x 100 mL) and then dried with Na_2SO_4. Concentration and chromatography (MeOH:CH_2Cl_2, 1:6) provided triol **1.131** (353 mg, 90 %) as a colorless oil.

To a solution of triol **1.131** (0.26 g, 1.8 mmol) in CH_2Cl_2 (10 mL) at rt was added benzaldehyde dimethyl acetal (0.30 mL, 2.0 mmol) followed by 10-camphorsulfonic acid (41mg, 0.18 mmol). After stirring at reflux overnight, the reaction was quenched with sat. $NaHCO_3$ (aq., 10 mL), extracted with CH_2Cl_2 (5 x 100 mL) and dried with Na_2SO_4. Concentration and chromatography (hexanes:ethyl acetate, 5:1 to 3:1) provided **1.132** (360 mg, 87%) as a colorless oil. R_f 0.33 (hexanes:ethyl acetate, 3:1); $[\alpha]_D^{20}$ = +3.03 (*c* =

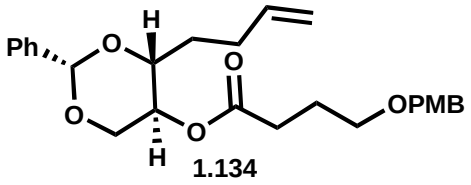
0.13, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.59 (dd, *J* = 6.8, 1.4 Hz, 2 H), 7.15-7.06 (m, 3 H), 5.80 (dddd, *J* = 17.1, 9.7, 6.8, 6.8 Hz, 1 H), 5.27 (s, 1H), 5.04 (dd, *J* = 17.1, 1.47 HZ, 1 H), 4.97 (dd, *J* = 10.25, 0.98 Hz, 2 H), 4.0 (dd, *J* = 9.3, 4.4 Hz, 1 H), 3.34-3.82 (m, 3 H), 2.33 (m, 1 H), 2.32-2.15 (m, 3 H), 1.92 (m, 1 H); ^{13}C NMR (125 MHz, C_6D_6) δ 139.2, 138.9, 129.0, 128.7, 128.5, 126.0, 115,1, 101.3, 81,6, 71.7, 66.2, 31.5, 29.7; IR (neat) 3627, 1387, 1605, 1004 cm^{-1}; LRMS (APCI) calcd for $C_{14}H_{22}NO_3$ 252.2 ($M+NH_4^+$), found 251.8.



1.133

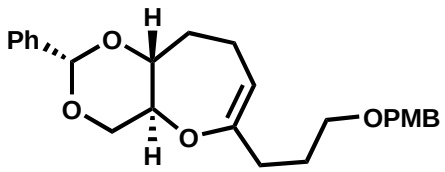
4-(4-methoxybenzyloxy)butanoic acid (1.133). To a solution of NaH (1.42 g, 59.1 mmol) in THF (175 mL) at 0 °C was added 1,4-butanediol (5.0 mL, 56 mmol) dropwise. Then *p*-(methoxy) benzyl chloride (8.0 mL, 56 mmol) was added dropwise followed by tBu$_4$NI (2.29 g, 6.20 mmol). After heating at reflux overnight, the reaction was quenched with sat. $NaHCO_3$ (aq., 20 mL), extracted with ethyl acetate (5 x 100 mL) and dried with Na_2SO_4. Concentration and chromatography (hexanes:ethyl acetate, 3:1) provided 4-(*p*-methoxybenzyloxy)butan-1-ol **1.136** (7.70 g, 65%) as a colorless oil.

To a solution of 4-(*p*-methoxybenzyloxy)butan-1-ol **1.136** (2.0 g, 9.5 mmol) in acetone (120 mL) at -10 °C was added Jones reagent (10.0 mL of a 2.78 M solution in acetone, 27.8 mmol) slowly. After stirring for 1.5 h, the reaction was quenched with *i*-PrOH and extracted with EtOAc. The extract was washed with brine and dried with Na_2SO_4. Concentration and chromatography (hexanes:ethyl acetate, 1:1) provided 4-(*p*-methoxybenzyloxy)butyric acid **1.133** (1.5 g, 70%) as a colorless oil whose spectrum matched that published previously.[47]



1.134

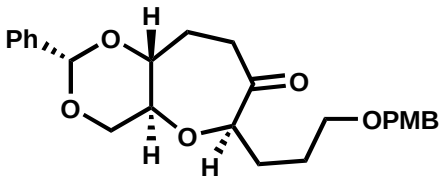
(4R,5S)-4-(but-3-enyl)-2-phenyl-1,3-dioxan-5-yl 4-(4-methoxybenzyloxy) butanete (1.134). To a solution of **1.132** (0.10 g, 0.43 mmol) in CH_2Cl_2 (2.0 mL) at rt was added the acid **1.133** (0.24 g, 1.1 mmol) followed by 1,3-dicyclohexylcarbodiimide (0.26 g, 1.3 mmol) and DMAP (0.13 g, 1.1 mmol). After stirring at rt for 12 h, the reaction mixture was filtered. The filtrate was washed with sat. $NaHCO_3$ (aq., 2.0 mL) and the aqueous phase was extracted with CH_2Cl_2 (5 x 20 mL). The organic extracts were dried with Na_2SO_4. Concentration and chromatography (hexanes:ethyl acetate, 10:1 to 5:1) provided **1.134** (0.154 g, 82%) as a colorless oil. R_f 0.50 (hexanes:ethyl acetate, 3:1); $[\alpha]_D^{20}$ = +22.4 (*c* = 1.12, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.54 (d, *J* = 7.8 Hz, 2 H), 7.19-7.12 (m, 5 H), 6.78 (d, *J* = 8.3 Hz, 2 H), 5.72 (dddd, *J* = 17.1, 10.3, 6.8Hz, 1 H), 5.28 (s, 1 H), 4.99 (dd, *J* = 17.09, 0.98 Hz, 1 H), 4.94-4.89 (m, 2 H), 4.31 (dd, *J* = 10.7, 5.4 Hz, 1 H), 4.24 (s, 2 H), 3.58 (dt, *J* = 9.3, 2.4 Hz, 1 H), 3.35-3.31 (m, 4 H), 3.22 (t, *J* = 5.9 Hz, 2 H), 2.24-2.21 (m, 3 H), 2.10 (m, 1H), 1.78-1.72 (m, 3 H), 1.50 (m, 1 H); ^{13}C NMR (125 MHz, C_6D_6) δ 172.0, 159.7, 138.6, 138.3, 131.8, 131.0, 129.4, 128.9, 127.7, 126.7, 115.1, 114.4, 114.1, 101.4, 78.6, 72.7, 68.7, 68.2, 67.0, 54.8, 31.3, 31.2, 29.2, 25.5; IR (neat) 2930, 1738, 1607, 1453, 1256, 1169, 1099, 1029 cm^{-1}; LRMS (APCI) calcd for $C_{26}H_{32}O_6$ 458.2 (M+NH_4^+), found 457.7.



1.138

(4aS,9aR,Z)-6-(3-(4-methoxybenzyloxy)propyl)-2-phenyl-4a,8,9,9a-tetrahydr-o-4H-[1,3]dioxino[5,4-b]oxepine (1.138). To a solution of $TiCl_4$ (0.80 mL, 7.3 mmol) in CH_2Cl_2 (53.2 mL) at 0 ^oC was added THF (3.83 mL, 43.6 mmol) dropwise. The solution was stirred at 0 ^oC for 0.2 h and then TMEDA (6.55 mL, 43.6 mmol) was added dropwise to the light-yellow solution. The ice bath was removed and after 0.3 h Zn dust (1.07 g, 16.4 mmol) was added followed by $PbCl_2$ (0.24 g, 0.86 mmol). Over 5 min, the reaction slurry turned from green to blue to blue-green at which time a solution of **1.134** (0.10 g, 0.23 mmol), CH_3CHBr_2 (0.50 ml, 7.3 mmol), and CH_2Cl_2 (10 mL) was added via a cannula. The resulting mixture was stirred rapidly and heated at reflux for 1.5 h. Then the reaction mixture was cooled to 0 ^oC and stirred with sat. K_2CO_3 (aq., 1.8 mL) for 0.5 h. The mixture was filtered and the residue was washed with 1:1 hexanes:ethyl acetate (3 x 40 mL). The filtrate was combined and concentrated. Flash chromatography (hexanes:ethyl acetate, 10:1 w/ 1% Et_3N) provided cyclic enol ether **1.138** (63 mg, 68%) as a colorless oil. R_f 0.60 (hexanes:ethyl acetate, 3:1); $[\alpha]_D^{20}$ = -25.0 (*c* = 0.12, THF); ^1H NMR (500 MHz, C_6D_6) δ 7.65 (d, *J* = 7.8 Hz, 2 H), 7.32-7.13 (m, 5 H), 6.8 (d, *J* = 8.8 Hz, 2 H), 5.34 (s, 1 H), 4.71 (dd, *J* = 7.8, 3.9 Hz, 1 H), 4.32 (s, 2 H), 4.27 (dd, *J* = 10.7, 5.4 Hz, 1 H), 3.6 (t, *J* = 10.5 Hz, 1 H), 3.52 (dt, *J* = 9.8, 3.9 Hz, 1 H), 3.42 (m, 1 H), 3.31-3.29 (m, 5 H), 2.11 (m, 2 H), 1.95 (m, 2 H), 1.75-1.72 (m, 3 H), 1.50 (m, 1 H); ^{13}C NMR (125 MHz, C_6D_6) δ 159.4, 139.0, 131.5, 129.6, 129.0, 128.5, 128.4, 127.0, 114.2, 108.3, 101.3, 83.1, 75.6, 72.9, 69.5, 69.4, 54.9, 32.9, 32.7, 27.7, 21.4; IR (neat) 2921,

2852, 1464, 1261, 752 cm^{-1}; LRMS (APCI) calcd for $C_{25}H_{31}O_5$411.2 ($M+H^+$), found 411.0.

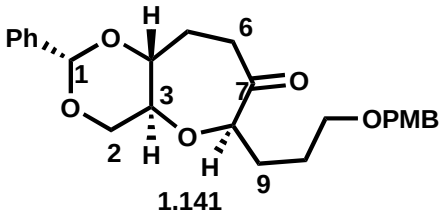


1.141

(4aS,6R,9aR)-6-(3-(4-methoxybenzyloxy)propyl)-2-phenyl-tetrahydro-6H[1,3] dioxino[5,4-b]oxepin-7(8H)-one (1.141). To **1.138** (50. mg, 0.12 mmol) in CH_2Cl_2 (20 mL) at –78 °C was added dimethyl dioxirane (2.4 mL of a 0.10 M solution in CH_2Cl_2, 0.24 mmol) dropwise. The reaction was warmed to 0 °C and concentrated. The colorless oil was taken up in CH_2Cl_2 (20 mL), cooled to -78 °C. *i*Bu_2AlH (0.24 mL of a 1.0 M solution in hexanes, 0.24 mmol) was added at once. After stirring at -78 °C for 10 min, the reaction was warmed up to 0 °C over 1 h. The reaction was quenched with sat. NH_4Cl (aq., 2.5 mL). The phases were separated. The aqueous phase was extracted with CH_2Cl_2 (5 x 50 mL) and dried with Na_2SO_4. Concentration and chromatography (hexanes:ethyl acetate, 5:1 to 3:1) provided the secondary alcohol **1.140** (40.7 mg, 78%) as a colorless oil.

To the alcohol (30 mg, 0.070 mmol) from above in CH_2Cl_2 (5.0 mL) at rt was added 4Å MS (30 mg), NMO (14. mg, 0.14 mmol), then TPAP (ca. 2mg). After stirring at rt for 2 h, the reaction mixture was filtered through neutralized silica. Concentration and chromatography (hexanes:ethyl acetate, 10:1 to 4:1) provided ketone **1.141** (24 mg, 80%) as a colorless oil. R_f 0.32 (hexanes:ethyl acetate, 3:1); $[\alpha]_D^{20}$ = +48.0 (*c* = 0.17, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.61 (d, *J* = 6.8 Hz, 2 H), 7.22-7.11 (m, 5 H), 6.8 (d, *J* = 8.8 Hz, 2 H), 5.27 (s, 1 H), 4.29 (s, 2 H), 4.02 (dd, *J* = 10.8, 5.4), 3.56 (m, 1 H), 3.45

(t, *J* = 10.3 Hz, 1 H), 3.29 (s, 3 H), 3.26 (m, 3 H), 2.85 (dt, *J* = 9.8, 5.4 Hz, 1 H), 2.42 (m, 1 H), 2.11 (m, 1 H), 1.81 (m, 1 H), 1.68 (m, 4 H), 1.49 (m, 1 H); ^{13}C NMR (125 MHz, C_6D_6) δ 213.3, 159.7, 138.6, 131.2, 129.4, 129.0, 126.7, 114.1, 101.2, 87.2, 81.1, 76.1, 72.4, 69.4, 69.3, 54.8, 36.2, 30.0, 29.5, 26.0; IR (neat) 2839, 1651, 1452, 1022 cm^{-1}; LRMS (APCI) calcd for $C_{25}H_{34}NO_6$ 444.2 ($M+NH_4^+$), found 443.7.



1.141

Summary of COSY spectrum for **1.141**:

Proton at 4.02 ppm (H-2) shows crosspeaks with protons at 3.45 ppm (H-2) and 2.85 ppm (H-3)

Proton at 3.56 ppm (H-8) shows crosspeak with proton at 1.68 ppm (H-9)

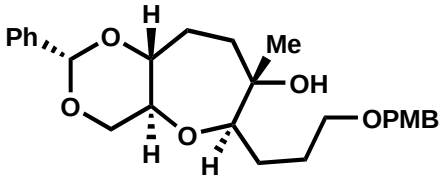
Proton at 3.44 ppm (H-2) shows crosspeak with proton at 4.02 ppm (H-2)

Proton at 3.26 ppm (H-10) shows crosspeak with proton at 1.68 ppm (H-9)

Proton at 2.85 ppm (H-3) shows crosspeaks with protons at 4.02 ppm (H-2), 3.45 ppm (H-2) and 3.26 ppm (H-4)

Summary of 1D nOe difference experiments for **1.141**:

Irradiation at 2.85 ppm (H-3) resulted in enhancement at 3.56 ppm (H-8)

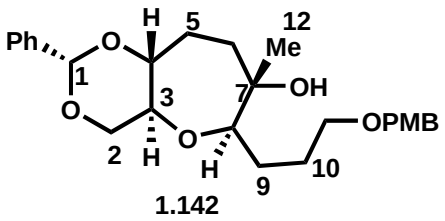


1.142

(4aS,6R,7S,9aR)-6-(3-(4-methoxybenzyloxy)propyl)-7-methyl-2-phenyl-hexa-hydro-4H-[1,3]dioxino[5,4-b]oxepin-7-ol (1.142). To a solution of **1.141** (20 mg, 0.047

mmol) in toluene (2.5 mL) at -78 °C was added MeMgBr (0.063 mL of a 3.0 M solution in ether, 0.18 mmol). After stirring at -78 °C for 10 min, the reaction was warmed up to 0 °C and kept at this temperature for 1 h. The reaction was quenched with sat. NH_4Cl (aq., 2.5 mL). The phases were separated. The aqueous phase was extracted with CH_2Cl_2 (5 x 10 mL) and dried with Na_2SO_4. Concentration and chromatography (hexanes:ethyl acetate, 5:1 to 3:1) provided **1.142** (15.7 mg, 86%) and **1.143** (2.0 mg, 11%) as colorless oils.

Data for **1.142**: R_f 0.18 (hexanes:ethyl acetate, 3:1); $[\alpha]_D^{20}$ = +0.8 (*c* = 0.25, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.66 (d, *J* = 7.3 Hz, 2 H), 7.26-7.15 (m, 5 H), 6.82 (d, *J* = 8.8 Hz, 2 H), 5.31 (s, 1 H), 4.35 (s, 2 H), 4.23 (dd, *J* = 10.0, 4.6 Hz, 1 H), 3.45 (t, *J* = 10.3 Hz, 1 H), 3.40-3.36 (m, 3 H), 3.30 (m, 4 H), 3.14 (dd, *J* = 10.8, 1.5 Hz, 1 H), 1.88-1.82 (m, 3 H), 1.70 (m, 1 H), 1.63-1.56 (m, 2 H), 1.50-1.41 (m, 2 H), 0.93 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 159.8, 139.1, 131.5, 129.6, 129.0, 128.5, 128.4, 127.0, 114.3, 101.6, 89.0, 83.4, 77.4, 74.5, 73.0, 70.3, 70.2, 54.9, 39.6, 28.1, 28.0, 27.7, 24.1; IR (neat) 3475, 1768, 1248, 1055 cm^{-1}; LRMS (APCI) calcd for $C_{26}H_{38}NO_6$ 460.3 ($M+NH_4^+$), found 459.9.



1.142

Summary of COSY spectrum for **1.142**:

Proton at 4.23 ppm (H-2) shows crosspeak with proton at 3.45 ppm (H-2)

Proton at 3.45 ppm (H-2) shows crosspeaks with protons at 3.30 ppm (H-3) and 4.23 ppm (H-2)

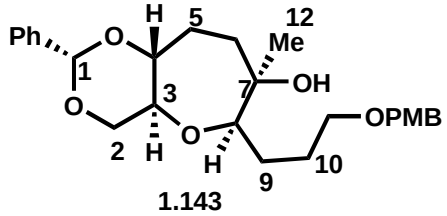
Proton at 3.30 ppm (H-3) shows crosspeaks with protons at 3.36 ppm (H-4) and 3.45 ppm (H-2)

Proton at 3.14 ppm (H-8) shows crosspeak with proton at 1.41 ppm (H-9)

Summary of 1D nOe difference experiments for **1.142**:

Irradiation at 0.92 ppm (CH_3-12) resulted in enhancement at 1.60 ppm (H-6) and 1.83 ppm (H-5)

Data for **1.143**: R_f 0.16 (hexanes:ethyl acetate 3:1); $[\alpha]_D^{20}$ = -3.6 (*c* = 0.03, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.68 (d, *J* = 7.8 Hz, 2 H), 7.26-7.13 (m, 5 H), 6.82 (d, *J* = 8.3 Hz, 2 H), 5.30 (s, 1 H), 4.34 (d, *J* = 6.4 Hz, 2 H), 4.21 (dd, *J* = 10.8, 4.9 Hz, 1 H), 3.46 (t, *J* = 10.3 Hz, 1 H), 3.40-3.34 (m, 2 H), 3.30 (s, 3 H), 3.27-3.24 (m, 1 H), 3.12 (dt, *J* = 9.7, 4.9 Hz, 1 H), 2.90 (dd, *J* = 10.3, 2.0 Hz, 1 H), 1.94 (m, 1 H), 1.83 (m, 1 H), 1.69-1.46 (m, 6 H), 0.89 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 159.9, 139.2, 131.5, 129.7, 129.0, 128.5, 128.4, 127.8, 127.6, 127.0, 114.3, 101.6, 89.3, 83.0, 78.3, 74.5, 73.0, 70.2, 70.1, 54.9, 39.6, 28.7, 27.4, 27.2, 26.8; IR (neat) 3475, 1768, 1247, 1055 cm^{-1}; LRMS (APCI) calcd for $C_{26}H_{38}NO_6$ 460.3 ($M+NH_4^+$), found 459.9.



1.143

Summary of COSY spectrum for **1.143**:

Proton at 4.21 ppm (H-2) shows crosspeak with proton at 3.46 ppm (H-2)

Proton at 3.46 ppm (H-2) shows crosspeaks with protons at 3.18 ppm (H-3) and 4.21 ppm (H-2)

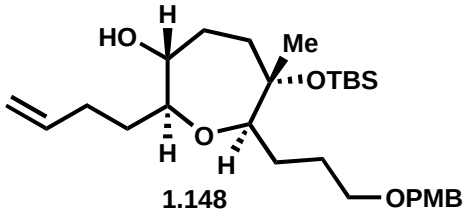
Proton at 3.12 ppm (H-3) shows crosspeaks with protons at 3.25 ppm (H-4), 3.46 ppm (H-2) and 4.21 ppm (H-2)

Proton at 2.90 ppm (H-8) shows crosspeak with proton at 1.6 ppm (H-9)

Summary of 1D nOe difference experiments for **1.143**:

Irradiation at 0.89 ppm (CH_3-12) resulted in enhancement at 1.6 ppm (H-6) and 2.90 ppm (H-8)

Irradiation at 2.90 ppm (H-8) resulted in enhancement at 0.89 ppm (H-12) and 3.12 ppm (H-3)



1.148

(2S,3R,6S,7R)-7-(3-(4-methoxybenzyloxy)propyl)-2-(but-3-enyl)-6-(tert-butyl dimethylsilyloxy)-6-methyloxepan-3-ol (1.148). To a solution of **1.142** (5.0 mg, 11 μmol) in CH_2Cl_2 (2.0 mL) at 0 ^oC was added NEt_3 (0.028 mL, 0.20 mmol) followed by TBSOTf (0.026 mL, 0.11 mmol) and DMAP (ca. 0.5mg). The reaction mixture was warmed to rt over 1 h at which time the reaction was quenched with sat. $NaHCO_3$ (aq., 3 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (5 x 10 mL).The extracts were dried with Na_2SO_4. Concentration and chromatography (hexanes:ethyl acetate, 50:1 to 10:1) provided protected alcohol **1.144** (5.6 mg, 90%) as a colorless oil.

To a solution of **1.144** (5.0 mg, 9.0 μmol) in MeOH (1 mL) at rt was added PPTS (2.5 mg, 10 μmol). After refluxing for 3 h, the reaction mixture was cooled to rt and the

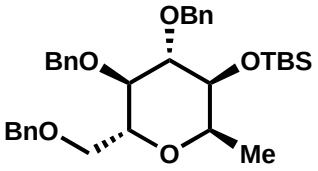
reaction was quenched with sat. $NaHCO_3$ (aq., 0.5 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (5 x 10 mL). The organic extracts were dried with Na_2SO_4. Concentration and chromatography (MeOH:CH_2Cl_2, 1:6) provided diol **1.145** (3.7 mg, 90 %) as a colorless oil.

To a solution of the diol **1.145** (2.0 mg, 4.3 μmol) from above in CH_2Cl_2 (1 mL) at -78 ^oC was added 2,6-lutidine (1.0 μl, 8.5 μmol) followed by Tf_2O (0.8 μl, 4.5 μmol). After 15 min, TESOTf (19 μl, 85 μmol) and 2,6-lutidine (20 μl, 0.17 mmol) were added and the reaction mixture was warmed to rt. After 0.5 h, the reaction mixture was cooled to -78 ^oC and the reaction was quenched with sat. $NaHCO_3$ (aq., 3 mL). The phases were separated were separated and the aqueous phase was extracted with CH_2Cl_2 (5 x 10 mL). The organic extracts were dried with Na_2SO_4 and concentrated. The yellow oil was passed through a short plug of silica (hexanes:ethyl acetate, 5:1) and immediately taken on to the next step.

A solution of the triflate from above in THF (0.5 mL) at -40 ^oC was added *via* cannula to a solution of allyl cuprate [Prepared from allyl magnesium chloride (0.66 mL of a 2.0 M solution in THF, 1.3 mmol) and CuI (0.14 g, 0.73 mmol) at -78 ^oC. The mixture was slowly warmed to 0 ^oC and stirred for 1 h]. The reaction mixture was stirred at -40 ^oC for 2 h, warmed to rt and quenched with sat. NH_4Cl (aq., 10 mL). The mixture was extracted with CH_2Cl_2 (5 x 10 mL) and dried with Na_2SO_4. Concentration and chromatography (hexanes:ethyl acetate, 5:1 to 3:1) provided protected alcohol **1.147** (2.0 mg, 75%) as acolorless oil.

To a solution of **1.147** from above in MeOH (0.5 mL) at 0 ^oC was added 10-camphorsulfonic acid (ca. 0.2 mg).The reaction mixture was warmed to rt over 1 h.The

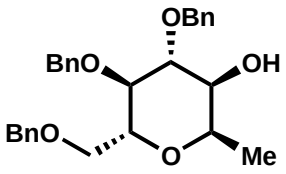
reaction was quenched with sat. $NaHCO_3$ (aq., 1 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (5 x 10 mL).The organic extracts were dried with Na_2SO_4. Concentration and chromatography (hexanes:ethyl acetate, 10:1 to 3:1) provided alcohol **1.148** (1.5 mg, 90%) as a colorless oil. R_f 0.51 (hexanes:ethyl acetate, 3:1); $[\alpha]_D^{20}$ = -13.8 (*c* = 0.014, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.26 (d, *J* = 8.8 Hz, 2 H), 6.82 (d, *J* = 8.8 Hz, 2 H), 5.88 (dddd, *J* = 16.6, 10.3, 6.4 Hz, 1 H), 5.10 (dd, *J* = 17.1, 1.9 Hz, 1 H), 5.00 (ddd, *J* = 10.3, 1.0, 1.0 Hz,1 H), 4.35 (s, 2 H), 3.42 (m, 2 H), 3.34 (dd, *J* = 10.7,1.5 Hz, 1 H), 3.30 (s, 3 H), 3.12 (m, 1 H), 2.48 (m, 1 H), 2.24 (m, 1 H), 2.01 (m, 1 H), 1.86 (m, 2 H), 1.80-1.50 (m, 7 H), 1.12 (s, 3 H), 0.97 (s, 9 H), 0.09 (d, *J* = 1.46 Hz, 6 H); ^{13}C NMR (125 MHz, C_6D_6) δ 159.6, 139.2, 131.5, 128.3, 114.7, 87.3, 77.7, 76.2, 72.7, 72.6, 67.1, 54.7, 37.6, 34.8, 30.7, 30.0, 28.0, 27.8, 26.0, 23.8, 18.3, -1.9, -2.0; IR (neat) 3365, 2924, 1612, 770 cm^{-1}; LRMS (ESI) calcd for $C_{28}H_{48}O_5SiNa$ 515.3 ($M+Na^+$), found 515.4.



1.199

((2R,3S,4S,5R,6R)-4,5-bis(benzyloxy)-6-(benzyloxymethyl)-2-methyl-tetrahydro-2H-pyran-3-yloxy)(tert-butyl)dimethylsilane (1.199). The general procedure for the DMDO epoxidation/ZnR_2 addition of tri-*O*-benzyl-D-glucal is given below. To a solution of **1.198** (20 mg, 0.048 mmol) and CH_2Cl_2 (1.0 mL) at 0 °C was added a solution of dimethyl dioxirane (0.72 mL of a 0.10 M solution in acetone, 0.072 mmol) dropwise. After 10 min, the reaction mixture was concentrated to give epoxide **1.191**.

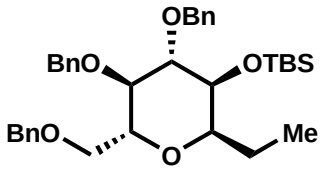
To a solution of epoxide **1.191** and CH_2Cl_2 (1.0 mL) at 0 °C was added dimethyl zinc (0.48 mL of a 1.0 M solution in heptane, 0.48 mmol) followed by a solution of TBSOTf (0.025 mL, 0.11 mmol) in CH_2Cl_2 (0.50 mL). After stirring at 0 °C for 2 h, the reaction was quenched with sat. $NaHCO_3$ (aq., 1.0 mL). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL). The extracts were combined, dried with Na_2SO_4, and concentrated. Flash chromatography (hexanes:ethyl acetate, 10:1) provided 24 mg (89%) of **1.199** as a colorless oil. R_f 0.78 (hexanes:ethyl acetate, 3:1); $[\alpha]_D^{20}$ = +21.9 (*c* = 0.40, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 7.40 (d, *J* = 6.8 Hz, 2 H), 7.32 (d, *J* = 7.8 Hz, 2 H), 7.23-7.06 (m, 11 H), 4.92-4.86 (m, 3 H), 4.65 (d, *J* = 11.2 Hz, 1 H), 4.49 (d, *J* = 12.2 Hz, 1 H), 4.42 (d, *J* = 12.2 Hz, 1 H), 4.19-4.14 (dq, *J* = 6.8 Hz, 1 H), 3.93-3.90 (dd, *J* = 9.3,6.4 Hz, 1 H), 3.83-3.75 (m, 3 H), 3.72-3.67 (m, 2 H), 1.26 (d, *J* = 6.8 Hz, 3 H), 0.89 (s, 9 H), 0.02 (s, 3 H), -0.08 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 139.7, 139.4, 139.1, 128.8, 128.5, 128.4, 127.8, 127.6, 127.4, 127.3, 83.3, 79.3, 75.4, 75.0, 73.8, 73.6, 72.7, 72.2, 70.0, 26.0, 18.1, 12.0, -4.6, -4.8; IR (neat) 3031, 2929, 2857, 1454, 1265, 1101, 864 cm^{-1}; LRMS (ESI) calcd for $C_{34}H_{46}O_5SiNa$ 585.3 (M+Na$^+$), found 585.3.



1. 200

(2R,3S,4R,5R,6R)-4,5-bis(benzyloxy)-6-(benzyloxymethyl)-2-methyl-tetrahydro-2H-pyran-3-ol (1.200). The general procedure for the deprotection of TBS group is given here. To a solution of **1.199** (24 mg, 0.043 mmol) and THF (1.0 mL) at 0 °C was added TBAF (0.22 mL of a 1.0 M solution in THF, 0.22 mmol). The reaction mixture was warmed up to rt over 1 h. After stirring at rt for 3 h, the reaction was quenched with

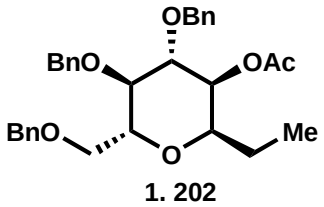
aq. NH_4Cl (sat., 1.0 mL) at 0 °C. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The extracts were combined, dried with Na_2SO_4, and concentrated. Flash chromatography (hexanes:ethyl acetate, 3:1) gave 15.5 mg (81%) of known alcohol **1.200** as a colorless oilwhose spectrum matched that reported previously.[49(a)]



1. 201

((2R,3S,4S,5R,6R)-4,5-bis(benzyloxy)-6-(benzyloxymethyl)-2-ethyl-tetrahydro-2H-pyran-3-yloxy)(tert-butyl)dimethylsilane (1.201). According to the general procedure as described for the preparation of compound **1.199,** epoxide **1.191** was generated from **1.198** (27 mg, 0.065 mmol), CH_2Cl_2 (1.4 mL) and a solution of dimethyl dioxirane (0.97 mL of a 0.10 M solution in acetone, 0.10 mmol). Then epoxide **1.191** was treated with diethyl zinc (0.65 mL of a 1.0 M solution in hexane, 0.65 mmol), CH_2Cl_2 (1.4 mL) and a solution of TBSOTf (0.034 mL, 0.14 mmol) in CH_2Cl_2 (0.68 mL) to give 32 mg (86%) of **1.201** as a colorless oil after flash chromatography (hexanes:ethyl acetate, 10:1). R_f 0.78 (hexanes:ethyl acetate, 3:1); $[\alpha]_D^{20}$ = +20.6 (*c* = 0.34, CH_2Cl_2,); ^{1}H NMR (500 MHz, C_6D_6) δ 7.41 (d, *J* = 7.3 Hz, 2 H), 7.32 (d, *J* = 7.8 Hz, 2 H), 7.23-7.04 (m, 11 H), 4.94-4.87 (m, 3 H), 4.62 (d, *J* = 11.2 Hz, 1 H), 4.50 (d, *J* = 12.2 Hz, 1 H), 4.41 (d, *J* = 12.2 Hz, 1 H), 3.98 (dd, *J* = 8.8, 5.9 Hz, 1 H), 3.91-3.87 (m, 1 H), 3.80-3.74 (m, 1 H), 3.73-3.66 (m, 3 H), 3.64-3.61 (m, 1 H), 1.83-1.77 (m, 1 H), 1.73-1.65 (m, 1 H), 1.03 (t, *J* = 7.3 Hz, 3 H), 0.90 (s, 9 H), 0.04 (s, 3 H), -0.06 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 139.7, 139.4, 139.1, 128.5, 128.4, 127.8, 127.6, 127.4, 127.3, 83.7, 79.3, 78.3, 75.3, 75.0, 74.0,

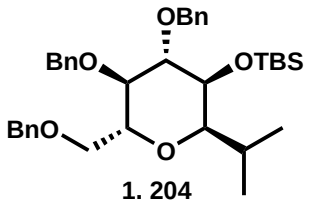
73.6, 71.8, 70.1, 26.0, 18.1, 17.6, 10.3, -4.6, -4.7; IR (neat) 3030, 2929, 2856, 1454, 1359, 1107, 837 cm^{-1}; LRMS (ESI) calcd for $C_{35}H_{48}O_5SiNa$ 599.3 ($M+Na^+$), found 599.3.



1. 202

(2R,3S,4R,5R,6R)-4,5-bis(benzyloxy)-6-(benzyloxymethyl)-2-ethyl-tetrahydro -2H-pyran-3-yl acetate (1.202). According to the general procedure as described for the preparation of compound **1.200**, TBAF (0.28 mL of a 1.0 M solution in THF, 0.28 mmol), THF (1.3 mL) and **1.201** (32 mg, 0.055 mmol) afforded the corresponding alcohol. The crude product was used directly without purification.

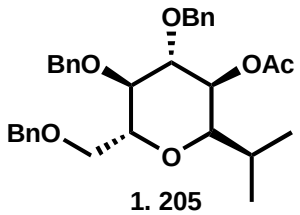
To a solution of the alcohol from above in CH_2Cl_2 (0.50 mL) at rt wasadded acetic anhydride (0.042 mL, 0.44 mmol), (i-Pr)$_2$NEt (0.077 mL, 0.44 mmol), and DMAP (ca. 5 mg). After stirring 1 h, the reaction was quenched with sat. NH_4Cl (aq., 1.0 mL). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL). The extracts were combined, dried with Na_2SO_4, and concentrated. Flash chromatography (hexanes:ethyl acetate, 5:1) provided 21 mg (75% for two steps) of known acetate **1.202** as a colorless oil whose spectrum matched that reported previously.[48(b)]



1. 204

((2R,3S,4S,5R,6R)-4,5-bis(benzyloxy)-6-(benzyloxymethyl)-2-isopropyl-tetra-hydro-2H-pyran-3-yloxy)(tert-butyl)dimethylsilane (1.204). According to the general

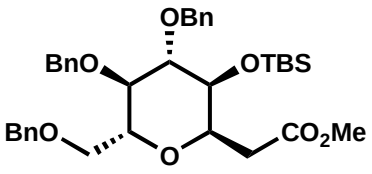
procedure as described for the preparation of compound **1.199**, tri-O-benzyl-D-glucal **1.198** (23 mg, 0.055 mmol), CH_2Cl_2 (1.2 mL) and a solution of dimethyl dioxirane (0.83 mL of a 0.10 M solution in acetone, 0.083 mmol) afforded epoxide **1.191** which reacted with diisopropyl zinc (0.55 mL of a 1.0 M solution in toluene, 0.55 mmol), CH_2Cl_2 (1.2 mL) and a solution of TBSOTf (0.029 mL, 0.12 mmol) in CH_2Cl_2 (0.58 mL) to give 26 mg (80%) of **1.204** as a colorless oil after flash chromatography (hexanes:ethyl acetate, 10:1). R_f 0.76 (hexanes:ethyl acetate, 3:1); $[\alpha]_D^{20}$ = +15.9 (*c* = 0.11, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 7.36 (d, *J* = 7.8 Hz, 2 H), 7.32-7.31 (m, 2 H), 7.24-7.05 (m, 11 H), 4.80-4.74 (m, 3 H), 4.57 (d, *J* = 11.7 Hz, 1 H), 4.49 (d, *J* = 12.2 Hz, 1 H), 4.42 (d, *J* = 12.2 Hz, 1 H), 4.08 (dd, *J* = 7.3, 4.4 Hz, 1 H), 3.92- 3.89 (m, 1 H), 3.84-3.77 (m, 2 H), 3.71-3.70 (m, 2 H), 3.54 (dd, *J* = 9.8, 3.9 Hz, 1 H), 2.12-2.14 (m, 1 H), 1.13 (d, *J* = 6.4 Hz, 3 H), 1.08 (d, *J* = 6.8 Hz, 3 H), 0.92 (s, 9 H), 0.06 (s, 3 H), 0.007 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ139.4, 139.3, 139.2, 128.5, 128.4, 128.3, 127.9, 127.8, 127.7, 127.6, 127.5, 82.8, 80.2, 78.9, 74.2, 73.6, 73.0, 70.3, 27.1, 26.2, 20.6, 20.3, 18.3, -4.3, -4.6; IR (neat) 3053, 2927, 2857, 1361, 1265, 1075, 837 cm^{-1}; LRMS (ESI) calcd for $C_{36}H_{50}O_5SiNa$ 613.3 ($M+Na^+$), found 613.3.



1. 205

(2R,3S,4S,5R,6R)-4,5-bis(benzyloxy)-6-(benzyloxymethyl)-2-isopropyl-tetra-hydro-2H-pyran-3-yl acetate (1.205). According to the general procedure for the preparation of alcohol **1.200**, TBAF (0.22 mL of a 1.0 M solution in THF, 0.22 mmol), **1.204** (26 mg, 0.044 mmol) and THF (1.0 mL) afforded the corresponding alcohol.

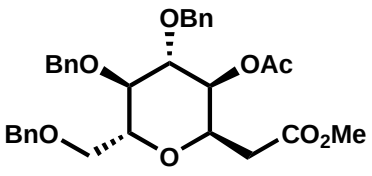
To a solution of the alcohol from above in CH_2Cl_2 (0.50 mL) at rt wasadded acetic anhydride (0.034 mL, 0.36 mmol), (*i*-Pr)$_2$NEt (0.063 mL, 0.36 mmol), and DMAP (ca. 5.0 mg). After stirring 1 h, the reaction was quenched with sat. NH_4Cl (aq., 1.0 mL). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL). The extracts were combined, dried with Na_2SO_4, and concentrated. Flash chromatography (hexanes:ethyl acetate, 5:1) provided 18 mg (79% for two steps) of acetate **1.205** as a colorless oil. R_f 0.53 (hexanes:ethyl acetate, 3:1); $[\alpha]_D^{20}$ = -9.2 (*c* = 0.12, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 7.31-7.29 (m, 5 H), 7.23-7.07 (m, 10 H), 5.32 (t, *J* = 3.42 Hz, 1 H), 4.69 (d, *J* = 11.7 Hz, 1 H), 4.60 (d, *J* = 12.2, Hz, 1 H), 4.53 (d, *J* = 11.7 Hz, 1 H), 4.46-4.38 (m, 3 H), 4.17 (ddd, *J* = 11.2, 4.9 Hz, 1 H), 3.97 (t, *J* = 4.4 Hz, 1 H), 3.78 (t, *J* =5.4 Hz, 1 H), 3.74 (d, *J* = 4.4 Hz, 2 H), 3.62 (dd, *J* = 9.3, 2.5 Hz, 1 H), 2.06-1.99 (m, 1 H), 1.65 (s, 3H), 1.11 (d, *J* = 6.4 Hz, 3 H), 0.77 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 170.0, 139.2, 139.0, 138.7, 128.6, 128.5, 128.4, 128.3, 128.2, 127.8, 127.7, 127.6, 127.5, 78.6, 75.8, 75.5, 73.9, 73.5, 72.9,72.8, 70.6, 69.8, 28.6, 20.6, 20.0, 18.6; IR (neat) 2958, 2918, 2856, 1738, 1714, 1454, 1368, 1237, 1096, 1073 cm^{-1}; LRMS (ESI) calcd for $C_{32}H_{38}O_6Na$ (M+Na$^+$) 541.3, found 541.2.



1. 208

Methyl 2-((2R,3S,4S,5R,6R)-4,5-bis(benzyloxy)-6-(benzyloxymethyl)-3-(tert-butyldimethylsilyloxy)-tetrahydro-2H-pyran-2-yl)acetate (1.208). According to the general procedure as described for the preparation of compound **1.199**, tri-O-benzyl-D-glucal **1.198** (36 mg, 0.086 mmol), CH_2Cl_2 (1.8 mL) and a solution of dimethyl dioxirane

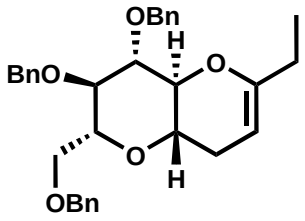
(1.3 mL of a 0.10 M solution in acetone, 0.13 mmol) afforded epoxide **1.191**. The epoxide was treated with CH_2Cl_2 (2.0 mL), tert-butyl(1-methoxyvinyloxy)dimethylsilane (0.32 g, 1.7 mmol) and a solution of TBSOTf (0.045 mL, 0.19 mmol) in CH_2Cl_2 (0.90 mL) at -78 °C. The reaction mixture was kept at -78 °C for 48 h, warmed up to -40 °C slowly and kept at -40 °C for another 24 h. The reaction mixture was warmed up to 0 °C and quenched with sat. $NaHCO_3$ (aq., 1.0 mL). The phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL). The extracts were combined, dried with Na_2SO_4, and concentrated. Flash chromatography (hexanes:ethyl acetate, 10:1) provided 42 mg (79%) of **1.208** as a colorless oil after flash chromatography (hexanes:ethyl acetate, 10:1). R_f 0.70 (hexanes:ethyl acetate, 3:1); $[\alpha]_D^{20}$ = -14.5 (*c* = 0.20, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 7.35-7.30 (m, 4 H), 7.21-7.03 (m, 11 H), 5.02 (d, *J* = 12.1 Hz, 1 H), 4.73 (t, *J* = 11.9 Hz, 2 H), 4.61 (d, *J* = 11.0 Hz, 1 H), 4.44 (d, *J* = 12.1 Hz, 1 H), 4.35 (d, *J* = 12.1 Hz, 1 H), 3.89 (dt, *J* = 9.3, 2.6 Hz, 1 H), 3.81 (t, *J* = 9.2 Hz, 1 H), 3.66 (d, *J* = 2.8 Hz, 2 H), 3.51 (t, *J* = 8.8 Hz, 1 H), 3.45- 3.41 (m, 2 H), 3.38 (s, 3 H), 2.95 (dd, *J* = 15.4, 2.8 Hz, 1 H), 2.57 (dd, *J* = 15.4, 9.5 Hz, 1 H), 0.90 (s, 9 H), 0.04 (s, 3 H), -0.04 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 173.2, 139.6, 139.0, 128.5, 128.4, 128.3, 127.8, 127.6, 127.2, 126.7, 87.0, 79.8, 79.3, 78.0, 75.0, 74.8, 74.3, 73.4, 69.1, 51.3, 38.0, 26.1, 18.2, -3.5, -4.3; IR (neat) 3063, 3030, 2951, 2928, 2857, 1743, 1256, 1089, 859, 837 cm^{-1}; LRMS (ESI) calcd for $C_{36}H_{48}O_7SiNa$ 643.3 (M+Na$^+$), found 643.3.



1. 208'

Preparation of acetate 1.208'. To a solution of **1.208** (32 mg, 0.052 mmol) and MeOH (1.0 mL) at rt was added p-toluenesulfonic acid monohydrate (32 mg, 0.17 mmol). After stirring at rt for 24 h, the reaction mixture was cooled to 0 °C and the reaction was quenched by the slow addition of sat. $NaHCO_3$ (aq., 2.0 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 10 mL), dried (Na_2SO_4), and concentrated. The crude product was used directly without further purification.

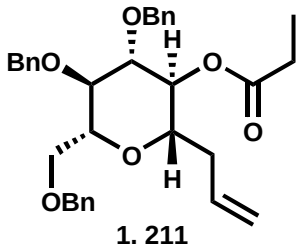
To a solution of the alcohol from above and CH_2Cl_2 (0.50 mL) at rt was added acetic anhydride (0.038 mL, 0.41 mmol), (*i*-Pr)$_2$NEt (0.071 mL, 0.41 mmol), and DMAP (ca. 5.0 mg). After stirring 1 h, the reaction was quenched with aq. NH_4Cl (sat., 1.0 mL). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL). The extracts were combined, dried with Na_2SO_4, and concentrated. Flash chromatography (hexanes:ethyl acetate, 10:1) gave 23 mg (80% for two steps) of acetate **1.208'** as a colorless oil. R_f 0.47 (hexanes:ethyl acetate, 3:1); $[\alpha]_D^{20}$ = +11.6 (*c* = 0.11, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 7.31-7.25 (m, 3 H), 7.20 (d, *J* = 7.3 Hz, 2 H), 7.15-7.05 (m, 10 H), 5.33 (dd, *J* = 7.8, 4.9 Hz, 1 H), 4.89 (ddd, *J* = 8.8, 5.4 Hz, 1 H), 4.66-4.59 (m, 3 H), 4.47 (d, *J* = 11.7 Hz, 1 H), 4.43 (d, *J* = 11.7 Hz, 1 H), 4.35(d, *J* = 11.7 Hz, 1 H), 3.88 (ddd, *J* = 8.3, 3.9 Hz, 1 H), 3.76 (t, *J* = 7.8 Hz, 1 H), 3.70-3.66 (m, 3 H), 3.31 (s, 3 H), 2.63 (dd, *J* = 15.1, 8.8 Hz, 1 H), 2.43 (dd, *J* = 15.1, 5.9 Hz, 1 H), 1.53 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 170.6, 169.3, 139.0, 128.6, 128.5, 128.3, 127.9, 127.8, 127.7, 127.6, 127.4, 79.8, 77.5, 74.3, 73.8, 73.6, 72.1, 69.6, 69.5, 51.3, 34.0, 20.3; IR (neat) 3061, 3031, 2952, 2918, 2857, 1744, 1713, 1453, 1363, 1226, 1087 cm^{-1}; LRMS (ESI) calcd for $C_{32}H_{36}O_8Na$ 571.2 (M+Na$^+$), found 571.2.



1. 209

(2R,3R,4S,4aS,8aS)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-6-ethyl-2,3,4,4a, 8,8a-hexahydropyrano[3,2-b]pyran (1.209). An oven dried two-necked flask fitted with a condenser was cooled to 0 °C and charged with CH_2Cl_2 (31. mL) followed by $TiCl_4$ (0.38 mL, 3.4 mmol). To the resulting solution was added THF (1.8 mL, 20. mmol) dropwise at which time the solution turned yellow. The addition of THF was followed by the dropwise addition of TMEDA (3.1 mL, 21 mmol) resulting in the formation of a brown solution. The ice bath was removed and the mixture was allowed to stir at rt for 20 min. Activated Zn dust (0.50 g 7.8 mmol) and $PbCl_2$ (0.11 g, 0.40 mmol) were then added. The resulting mixture went through a series of color changes from brown to green to purple and finally to blue-green over the course of 3-5 min. To the slurry was transferred a solution of ester **1.211** (0.10 g, 0.19 mmol) and CH_3CHBr_2 (0.31 mL, 3.4 mmol) in CH_2Cl_2 (2.0 mL + 2.0 mL rinse) via cannula. The reaction mixture was then heated to reflux for 4 h. Following this time period the mixture was cooled to 0 °C and quenched with sat K_2CO_3 (aq., 1.2 mL). After stirring for 30 min at 0 °C, the resulting mixture was filtered. The residue was washed with 1:1 hexanes:ethyl acetate (3 x 40 mL). The filtrate was combined and concentrated. The resulting residue was purified by flash chromatography (hexanes:ethyl acetate, 100:1 to 10:1) to give 0.075 g (80%) of cyclic enol ether **1.209** as a colorless oil. R_f 0.70 (hexanes:ethyl acetate, 3:1); $[\alpha]_D^{20}$ = +44.2 (*c* = 0.33, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 7.45 (d, *J* = 7.3 Hz, 2 H), 7.28-7.25 (m, 4

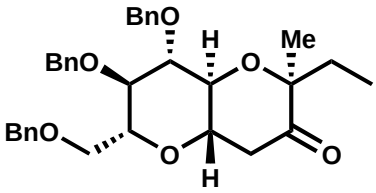
H), 7.20-7.04 (m, 9 H), 5.13 (d, *J* = 11.7 Hz, 1 H), 4.98 (d, *J* = 11.7 Hz, 1 H), 4.85 (d, *J* = 11.7 Hz, 1 H), 4.60 (d, *J* = 11.2 Hz, 1 H), 4.44 (d, *J* = 11.7 Hz, 1 H), 4.35 (d, *J* = 12.2 Hz, 1 H), 4.27-4.26 (m, 1 H), 3.80-3.73 (m, 2 H), 3.69-3.66 (m, 3 H), 3.45 (ddd, *J* = 8.8, 3.4, 2.0 Hz, 1 H), 3.3 (ddd, *J* = 9.3, 6.4 Hz, 1 H), 2.26-2.20 (m, 1 H), 2.18-2.12 (m, 1 H), 1.96 (q, *J* = 7.3 Hz, 2 H), 0.98 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2, 138.8, 138.2, 138.0, 128.3, 128.0, 127.9, 127.6, 127.5, 91.9, 84.3, 79.3, 78.8, 77.4, 75.2, 74.9, 73.5, 72.3, 69.1, 27.3, 26.5, 11.6; IR (neat) 3063, 3030, 2967, 2916, 2856, 1677, 1496, 1453, 1361, 1318, 1109, 921 cm^{-1}; LRMS (ESI) calcd for $C_{32}H_{36}O_5Na$ 523.3 ($M+Na^+$), found 523.2.



1. 211

(2S,3S,4S,5R,6R)-2-allyl-4,5-bis(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2H-pyran-3-yl propionate (1.211). To a solution of **1.210** (0.10 g, 0.21 mmol) in CH_2Cl_2 (10 mL) was added propionic acid (20 mg, 0.27 mmol), DCC (0.13 g, 0.63 mmol) and DMAP (0.051 g, 0.42 mmol). After stirring at rt for 5 h, the reaction was quenched with sat. $NaHCO_3$ (aq., 10 mL). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL). The extracts were combined, dried with Na_2SO_4, and concentrated. Flash chromatography (hexanes:ethyl acetate, 5:1) provided 0.10 g of **1.211** (92%) as a colorless oil. R_f 0.63 (hexanes:ethyl acetate, 3:1); $[\alpha]_D^{20}$ = +12.0 (*c* = 0.10, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 7.31-7.29 (m, 3 H), 7.22-7.04 (m, 12 H), 5.98 (dddd, *J* = 17.0, 10.3, 7.0, 7.0 Hz, 1 H), 5.25 (t, *J* = 9.3 Hz, 1 H), 5.13-5.04 (m, 2 H),

4.78 (d, *J* = 11.5 Hz, 1 H), 4.73 (d, *J* = 11.4 Hz, 1 H), 4.63 (d, *J* = 11.7 Hz, 1 H), 4.52 (d, *J* = 11.2 Hz, 1 H), 4.47 (d, *J* = 12.3 Hz, 1 H), 4.41 (d, *J* = 12.3 Hz, 1 H), 3.69- 3.55 (m, 4 H), 3.36 (ddd, *J* = 9.3, 4.4, 2.0 Hz, 1 H), 3.29-3.24 (m, 1 H), 2.37-2.34 (m, 2 H), 2.01-1.90 (m, 2 H), 0.93 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 172.7, 139.3, 139.1, 134.5, 128.5, 128.5, 127.9, 127.8, 127.7, 127.6, 117.2, 85.2, 79.9, 78.7, 77.8, 75.0, 74.9, 73.8, 73.5, 69.4, 36.7, 27.7, 9.1; IR (neat) 3030, 2979, 2939, 2864, 1745, 1453, 1360, 1180, 1101,1083, 914 cm^{-1}; LRMS (ESI) calcd for $C_{33}H_{38}O_6Na$ 553.3 (M+Na$^+$), found 553.2.



1. 214

(2S,4aS,6R,7R,8S,8aS)-7,8-bis(benzyloxy)-6-(benzyloxymethyl)-2-ethyl-2-methyl-hexahydropyrano [3,2-b]pyran-3(2H)-one (1.214). The general procedure for the DMDO epoxidation/ZnR_2 addition of **1.209** is given below. To a solution of **1.209** (30 mg, 0.060 mmol) and CH_2Cl_2 (1.3 mL) at -78 °C was added a solution of dimethyl dioxirane (0.90 mL of a 0.10 M solution in acetone, 0.090 mmol) dropwise. After 5 min, the reaction was warmed to 0 °C and concentrated. The epoxide was taken up in THF (1.0 mL) at -78 °C. Dimethyl zinc (0.60 mL of a 1.0 M solution in heptane, 0.60 mmol) was added followed by a solution of TBSOTf (0.031 mL, 0.13 mmol) in THF (0.63 mL). The reaction mixture was warmed up to 0 °C over 1 h. The reaction was quenched with sat. $NaHCO_3$ (aq., 1.0 mL). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL). The extracts were combined, dried with Na_2SO_4, and

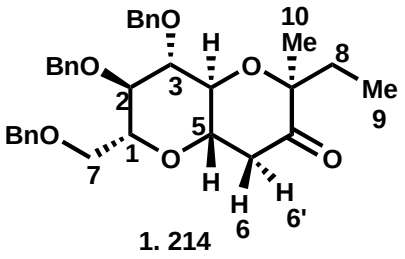
concentrated. Flash chromatography (hexanes:ethyl acetate, 10:1) provided 32 mg (82%) of **1.212** as a mixture.

For characterization purposes, **1.212** was converted to ketone **1.214** in two steps:

To a solution of **1.212** (30 mg, 0.046 mmol) and THF (1.0 mL) at 0 °C was added HF•pyridine (0.46 mL of a 1.0 M solution in THF, 0.46 mmol). After stirring overnight at rt, the reaction was diluted with CH_2Cl_2 (10 mL) and quenched with sat. $NaHCO_3$ (aq., 3 mL) at 0 °C. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL), dried with Na_2SO_4 and concentrated. The resulting alcohol was used directly without further purification.

To a solution of the alcohol from above inCH_2Cl_2 (5 mL) was added 4Å MS (20 mg), NMO (34 mg, 0.29 mmol) and TPAP (ca. 3.0 mg). After stirring at rt for 2 h, the reaction mixture was concentrated. Flash chromatography (hexanes:ethyl acetate, 5:1) gave 19 mg(76% for two steps) of ketone **1.214** as a colorless oil. R_f 0.55 (hexanes:ethyl acetate, 3:1); $[\alpha]_D^{20}$ = +43.9 (*c* = 0.09, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 7.39 (d, *J* = 7.8 Hz, 2 H), 7.31-7.27 (m, 4 H), 7.20-7.0 (m, 9 H), 5.0 (t, *J* = 10.7 Hz, 2 H), 4.76 (d, *J* = 11.2 Hz, 1 H), 4.65 (d, *J* = 11.2 Hz, 1 H), 4.42 (d, *J* = 11.7 Hz, 1 H), 4.34 (d, *J* = 12.2 Hz, 1 H), 3.80 (t, *J* = 9.3 Hz, 1 H), 3.69 (dd, *J* = 10.7, 3.9 Hz, 1 H), 3.64 (dd, *J* = 10.7, 2.0 Hz, 1 H), 3.59 (t, *J* = 8.8 Hz, 1 H), 3.46 (t, *J* = 9.3 Hz, 1 H), 3.33 (ddd, *J* = 9.8, 3.9, 1.5 Hz, 1 H), 3.04 (ddd, *J* = 11.2, 9.3, 5.9 Hz, 1 H), 2.70 (dd, *J* = 16.6, 5.9 Hz, 1 H), 2.33 (dd, *J* = 16.6, 11.7 Hz, 1 H), 1.88 (dq, *J* = 14.6, 7.3 Hz, 1 H), 1.55 (dq, *J* = 14.6, 7.3 Hz, 1 H), 0.96 (s, 3 H), 0.86 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 207.8, 139.7, 139.4, 138.9, 128.5, 128.3, 127.9, 127.8, 127.7, 127.5, 127.4, 84.3, 83.4, 79.5, 77.7, 75.8, 75.2,

74.9, 73.9, 73.6, 69.6, 43.0, 31.7, 21.1, 8.1; IR (neat) 3030, 2923, 1720, 1454, 1101, 698 cm^{-1}; LRMS (ESI) calcd for $C_{33}H_{38}O_6Na$ 553.3 ($M+Na^+$), found 553.2.



1. 214

Summary of COSY spectrum for **1.214**:

Proton at 1.55 ppm (H-8) shows crosspeaks with protons at 1.88 ppm (H-8) and 0.86 ppm (H-9)

Proton at 1.88 ppm (H-8) shows crosspeaks with protons at 1.55 ppm (H-8) and 0.86 ppm (H-9)

Proton at 2.33 ppm (H-6') shows crosspeaks with protons at 2.70 ppm (H-6) and 3.04 ppm (H-5)

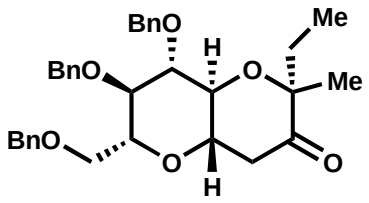
Proton at 2.70 ppm (H-6) shows crosspeaks with protons at 2.33 ppm (H-6') and 3.04 ppm (H-5)

Proton at 3.04 ppm (H-5) shows crosspeaks with protons at 2.33 ppm (H-6'), 2.70 ppm (H-6) and 3.46 ppm (H-4)

Proton at 3.46 ppm (H-4) shows crosspeaks with protons at 3.59 ppm (H-3), 3.04 ppm (H-5)

Summary of 1D nOe difference experiments for **1.214**:

Irradiation at 0.96 ppm (H-10) resulted in enhancement at 3.46 ppm (H-4)

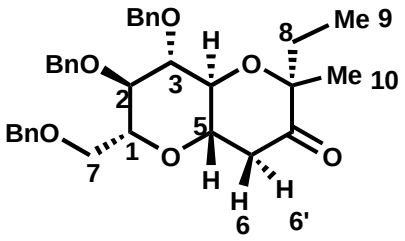


1. 217

(2R,4aS,6R,7R,8S,8aS)-7,8-bis(benzyloxy)-6-(benzyloxymethyl)-2-ethyl-2-methyl-hexahydropyrano[3,2-b]pyran-3(2H)-one (1.217). According to the general procedures for the preparation of **1.212**, enol ether **1.215** (25 mg, 0.051 mmol), CH_2Cl_2 (1.0 mL) and a solution of dimethyl dioxirane (0.77 mL of a 0.10 M solution in acetone, 0.077 mmol) afforded the epoxide which reacted with diethyl zinc (0.51 mL of a 1.0 M solution in hexane, 0.51 mmol), THF(1.0 mL) and a solution of TBSOTf (0.027 mL, 0.11 mmol) in THF(0.53 mL) to give 27 mg (81%) **1.216** as a mixture after flash chromatography (hexanes:ethyl acetate, 10:1).

For characterization purposes, **1.216** was converted to ketone **1.217** in two steps. According to the general procedures for the preparation of **1.214**, **1.216** (27 mg, 0.042 mmol) reacted with HF•pyridine (0.42 mL of a 1.0 M solution in THF, 0.42 mmol) to give the crude alcohol. The crude alcohol was reacted with 4Å MS (20 mg), NMO (31 mg, 0.26 mmol) and TPAP (ca. 3.0 mg) to give 17 mg (75% for two steps) of **1.217** as a colorless oil. R_f 0.56 (hexanes:ethyl acetate, 3:1); $[\alpha]_D^{20}$ = +67.7 (*c* = 0.13, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 7.41 (d, *J* = 7.3 Hz, 2 H), 7.28-7.25 (m, 4 H), 7.20-7.05 (m, 9 H), 5.06 (d, *J* = 11.2 Hz, 1 H), 5.0 (d, *J* = 11.2 Hz, 1 H), 4.79 (d, *J* = 11.2 Hz, 1 H), 4.65 (d, *J* = 11.2 Hz, 1 H), 4.41 (d, *J* = 11.7 Hz, 1 H), 4.32 (d, *J* = 12.2 Hz, 1 H), 3.83 (t, *J* = 8.8 Hz, 1 H), 3.69 (dd, *J* = 10.7, 3.9 Hz, 1 H), 3.62 (dd, *J* = 10.8, 2.0 Hz, 1 H), 3.57 (t, *J* = 8.8 Hz, 1 H), 3.43 (t, *J* = 9.3 Hz, 1 H), 3.31 (ddd, *J* = 9.8, 3.9, 2.0 Hz, 1 H), 3.02-2.97 (m, 1 H), 2.72 (dd, *J* = 15.6, 5.9 Hz, 1 H), 2.40 (dd, *J* = 15.6, 11.7 Hz, 1 H), 1.45 (dq, *J* =

14.6, 7.3 Hz, 1 H), 1.27 (s, 3 H), 1.12 (dddd, J = 19.5, 12.7, 7.3 Hz, 1 H), 0.74 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 207.0, 139.5, 139.3, 138.8, 128.5, 128.3, 127.9, 127.8, 127.7, 127.5, 84.4, 83.0, 79.6, 77.8, 75.3, 75.2, 74.5, 73.6, 69.5, 42.5, 26.3, 21.0, 6.6; IR (neat) 3032, 2923, 1721, 1454, 1363, 1101,739 cm^{-1}; LRMS (ESI) calcd for $C_{33}H_{38}O_6Na$ 553.3 ($M+Na^+$), found 553.2.



1. 217

Summary of COSY spectrum for **1.217**:

Proton at 1.12 ppm (H-8) shows crosspeaks with protons at 1.45 ppm (H-8') and 0.74 ppm (H-9)

Proton at 1.45 ppm (H-8') shows crosspeaks with protons at 1.12 ppm (H-8) and 0.74 ppm (H-9)

Proton at 0.74 ppm (H-9) shows crosspeaks with protons at 1.12 ppm (H-8) and 1.45 ppm (H-8')

Proton at 2.40 ppm (H-6') shows crosspeaks with protons at 2.72 ppm (H-6) and 2.99 ppm (H-5)

Proton at 2.72 ppm (H-6) shows crosspeaks with protons at 2.40 ppm (H-6') and 2.99 ppm (H-5)

Proton at 2.99 ppm (H-5) shows crosspeaks with protons at 2.40 ppm (H-6), 2.72 ppm (H-6) and 3.43 ppm (C-4)

Proton at 3.43 ppm (H-4) shows crosspeaks with protons at 3.57 ppm (H-3) and 2.99 ppm (H-5)

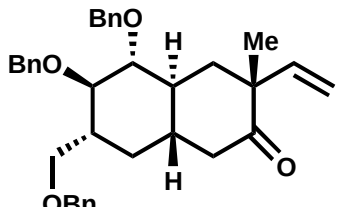
Proton at 3.57 ppm (H-3) shows crosspeaks with protons at 3.43 ppm (H-4) and 3.83 ppm (H-2)

Proton at 3.83 ppm (H-2) shows crosspeaks with protons at 3.31 ppm (H-1) and 3.57 ppm (H-3)

Summary of 1D nOe difference experiments for **1.217**:

Irradiation at 1.12 ppm (H-8) resulted in enhancement at 1.45 ppm (H-8') and 3.43 ppm (H-4)

Irradiation at 1.45 ppm (H-8') resulted in enhancement at 1.12 ppm (H-8), 2.40 ppm (H-6') and 3.43 ppm (H-4)

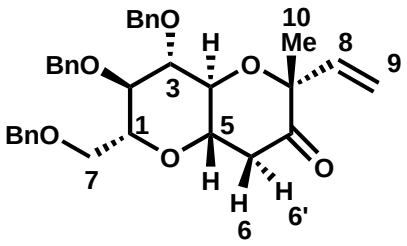


1. 219

(2R,4aS,6R,7R,8S,8aS)-7,8-bis(benzyloxy)-6-(benzyloxymethyl)-2-methyl-2-vinyl-hexahydr -opyrano[3,2-b]pyran-3(2H)-one (1.219). According to the general procedures for the preparation of **1.212**, enol ether **1.215** (28 mg, 0.058 mmol), CH_2Cl_2 (1.0 mL) and a solution of dimethyl dioxirane (0.86 mL of a 0.10 M solution in acetone, 0.086 mmol) afforded the epoxide which was taken up in THF (1.0 mL) and reacted with divinyl zinc (2.3 mL of a 0.25 M solution in THF, 0.58 mmol) to give 23 mg (75%) of **1.218** as colorless oils after flash chromatography (hexanes:ethyl acetate, 5:1).

Divinyl zinc (0.25 M solution in THF) was prepared according to the following procedure: vinly magnesium bromide (5.2 mL of a 1.0 M solution in THF, 5.2 mmol) was added to a solution of $ZnCl_2$ (2.6 mL of a 1.0 M solution in THF, 2.6 mmol) and THF (1.0 mL) at -30 ^oC. The reaction was warmed up to 0 ^oC and stirred at 0 ^oC for 0.5 h.

For characterization purposes, **1.218** was oxidized to give ketone **1.219**. To a solution of **1.218** (23 mg, 0.043 mmol) and CH_2Cl_2 (3.5 mL) was added 4Å MS (20 mg), NMO (25 mg, 0.22 mmol) and TPAP (ca. 3.0 mg). After stirring at rt for 2 h, the reaction was concentrated to give 20 mg (90%) of **1.219** as a colorless oil after flash chromatography (hexanes:ethyl acetate, 5:1). R_f 0.68 (hexanes:ethyl acetate, 3:1); $[\alpha]_D^{20}$ = +24 (*c* = 0.05, CH_2Cl_2); ^1H NMR (500 MHz, C_6D_6) δ 7.42-7.41 (m, 2 H), 7.26-7.25 (m, 4 H), 7.20-7.04 (m, 9 H), 5.56 (dd, *J* = 17.6, 10.7 Hz, 1 H), 5.12 (d, *J* = 18.1 Hz, 1 H), 5.05 (d, *J* = 11.2 Hz, 1 H), 4.97 (d, *J* = 11.2 Hz, 1 H), 4.89 (d, *J* = 10.8 Hz, 1 H), 4.83 (d, *J* = 11.7 Hz, 1 H), 4.62 (d, *J* = 11.2 Hz, 1 H), 4.39 (d, *J* = 12.2 Hz, 1 H), 4.31 (d, *J* = 12.2 Hz, 1 H), 3.76 (t, *J* = 8.8 Hz, 1 H), 3.71-3.59 (m, 4 H), 3.32 (ddd, *J* = 9.8, 3.9, 2.0 Hz, 1 H), 3.03 (ddd, *J* = 11.7, 9.8, 5.9 Hz, 1 H), 2.76 (dd, *J* = 15.6, 5.4 Hz, 1 H), 2.40 (dd, *J* = 16.1, 11.7 Hz, 1 H), 1.42 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 204.7, 139.5, 139.2, 138.8, 138.7, 128.5, 128.3, 128.2, 127.9, 127.8, 127.7, 127.6, 127.4, 116.8, 84.4, 79.6, 78.0, 76.7, 75.3, 74.5, 73.6, 69.5, 43.7, 25.1; IR (neat) 2918, 2850, 1722, 1453, 1363, 1100, 737 cm^{-1}; LRMS (ESI) calcd for $C_{33}H_{36}O_6Na$ 551.2 ($M+Na^+$), found 551.2.



1. 219

Summary of COSY spectrum for **1.219**:

Proton at 2.40 ppm (H-6') shows crosspeaks with protons at 2.76 ppm (H-6) and 3.03 ppm (H-5)

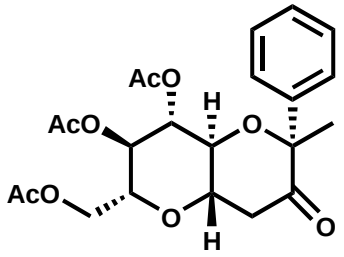
Proton at 2.76 ppm (H-6) shows crosspeaks with protons at 2.40 ppm (H-6') and 3.03 ppm (H-5)

Proton at 3.03 ppm (H-5) shows crosspeaks with protons at 2.76 ppm (H-6), 2.40 ppm (H-6') and 3.76 ppm (H-4)

Proton at 5.56 ppm (H-8) shows crosspeaks with protons at 5.12 ppm (H-9) and 4.89 ppm (H-9')

Summary of 1D nOe difference experiments for **1.219**:

Irradiation at 5.56 ppm (H-8) resulted in enhancement at 3.76 ppm (H-4), 5.12 ppm (H-9) and 4.89 ppm (H-9')



1. 222

(2R,4aS,6R,7R,8S,8aS)-7,8-bis(acetoxy)-6-(acetoxymethyl)-2-methyl-2-phenyl -hexahydropyrano[3,2-b]pyran-3(2H)-one (1.222). According to the general procedure

for the preparation of **1.212**, enol ether **1.215** (34 mg, 0.070 mmol), CH_2Cl_2 (1.4 mL) and a solution of dimethyl dioxirane (1.0 mL of a 0.10 M solution in acetone, 0.10 mmol) generated the epoxide which reacted with diphenyl zinc (2.8 mL of a 0.25 M solution in THF, 0.70 mmol) to give 27 mg (68%) of **1.220** as colorless oils after flash chromatography (hexanes:ethyl acetate, 5:1).

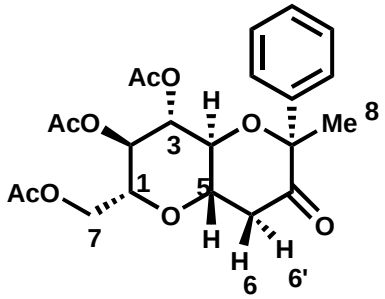
Diphenyl zinc (0.25 M solution in THF) was prepared according to the following procedures: PhMgBr (2.0 mL of a 1.0 M solution in THF, 2.0 mmol) was added to a solution of $ZnCl_2$ (1.0 mL of a 1.0 M solution in THF, 1.0 mmol) and THF (1.0 mL) at 0 ^oC. The reaction was stirred at 0 ^oC for 0.5 h and then warmed up to rt over 1 h.

For characterization purposes, **1.220** was converted to ketone **1.222** in three steps. To a solution of **1.220** (19 mg, 0.033 mmol) and CH_2Cl_2 (2.7 mL) was added 4Å MS (15 mg), NMO (19 mg, 0.17 mmol) and TPAP (ca. 2.0 mg). After stirring at rt for 2 h, the reaction was concentrated to give 16 mg (86%) of **1.221** as a colorless oil after flash chromatography (hexanes:ethyl acetate, 5:1).

To a solution of **1.221** (10 mg, 0.017 mmol) in dry ethanol (0.2 mL) was added Pd/C (5 wt%, 2 mg). The reaction mixture was stirred at rt under hydrogen atmosphere for 3 h. The reaction mixture was diluted with ethanol, passed through a bed of Celite and concentrated. The crude triol was used directly without further purification.

To a solution of the triol from above and CH_2Cl_2 (1.0 mL) at rt was added acetic anhydride (0.016 mL, 0.17 mmol), (i-Pr)$_2$NEt (0.030 mL, 0.17 mmol), and DMAP (ca. 1.0 mg). After stirring 5 h, the reaction was quenched with aq. NH_4Cl (sat., 1.0 mL). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The extracts were combined, dried with Na_2SO_4, and concentrated. Flash

chromatography (hexanes:ethyl acetate, 3:1) gave 5.0 mg (67% for two steps) of acetate **1.222** as a colorless oil. R_f 0.23 (hexanes:ethyl acetate, 3:1); $[\alpha]_D^{20}$ = +22.0 (*c* = 0.20, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 7.29 (d, *J* = 7.8 Hz, 2 H), 7.10 (d, *J* = 7.3 Hz, 1 H), 7.05-7.0 (m, 2 H), 5.43 (t, *J* = 9.5 Hz, 1 H), 5.06 (t, *J* = 9.8 Hz, 1 H), 4.20 (dd, *J* = 4.9, 12.7 Hz, 1 H), 3.95 (d, *J* = 12.2 Hz, 1 H), 3.56 (t, *J* = 9.8 Hz, 1 H), 3.25 (dd, *J* = 9.3, 3.9 Hz, 1 H), 2.92 (ddd, *J* = 16.6, 11.2, 5.4 Hz, 1 H), 2.70 (dd, *J* = 15.1, 5.4 Hz, 1 H), 2.20 (dd, *J* = 14.7, 12.7 Hz, 1 H), 1.85 (s, 3 H), 1.72 (3 H), 1.61 (3 H), 1.58 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 203.5, 169.9, 169.9, 169.7, 139.9, 129.4, 125.1, 85.7, 76.2, 74.8, 74.3, 73.1, 69.3, 62.2, 43.9, 32.3, 29.8, 28.1, 20.4; IR (neat) 2921, 2851, 1746, 1715, 1444, 1366, 1225, 1100 cm^{-1}; LRMS (ESI) calcd for $C_{22}H_{26}O_9Na$ 457.2 ($M+Na^+$), found 457.0.



1. 222

Summary of COSY spectrum for **1.222**:

Proton at 2.20 ppm (H-6') shows crosspeaks with protons at 2.70 ppm (H-6) and 2.92 ppm (H-5)

Proton at 2.70 ppm (H-6) shows crosspeaks with protons at 2.20 ppm (H-6') and 2.92 ppm (H-5)

Proton at 2.92 ppm (H-5) shows crosspeaks with protons at 2.70 ppm (H-6'), 2.20 ppm (H-6) and 3.56 ppm (H-4)

Proton at 3.56 ppm (H-4) shows crosspeaks with protons at 5.43 ppm (H-3) and 2.92 ppm (H-5)

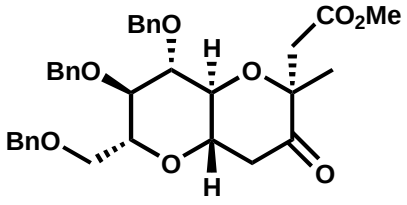
Proton at 5.43 ppm (H-3) shows crosspeaks with protons at 3.56 ppm (H-4) and 5.06 ppm (H-2)

Proton at 5.06 ppm (H-2) shows crosspeaks with protons at 5.43 ppm (H-3) and 3.25 ppm (H-1)

Proton at 4.20 ppm (H-7) shows crosspeaks with protons at 3.95 ppm (H-7') and 3.25 ppm (H-1)

Summary of 1D nOe difference experiments for **1.222**:

Irradiation at 3.56 ppm (H-4) resulted in enhancement at 5.06 ppm (H-2) and 7.05 ppm (Ph-H)

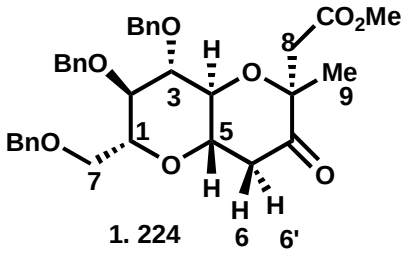


1. 224

Methyl 2-((2R,4aS,6R,7R,8S,8aS)-7,8-bis(benzyloxy)-6-(benzyloxymethyl)-2-methyl-3-oxo-octahydropyrano[3,2-b]pyran-2-yl)acetate (1.224). According to the general procedures for the preparation of **1.212**, enol ether **1.215** (41 mg, 0.084 mmol), CH_2Cl_2 (1.7 mL) and a solution of dimethyl dioxirane (1.3 mL of a 0.10 M solution in acetone, 0.13 mmol) afforded the epoxide which reacted with tert-butyl(1-methoxyvinyloxy)dimethylsilane (0.33 g, 1.8 mmol), THF (1.7 mL) and a solution of TBSOTf (0.046 mL, 0.19 mmol) in THF (0.9 mL) to give 45 mg (77%) of **1.223** as colorless oils after flash chromatography (hexanes:ethyl acetate, 10:1).

For characterization purposes, **1.223** was converted to ketone **1.224** in two steps. To a solution of **1.223** (45 mg, 0.059 mmol) and MeOH (1.2 mL) at rt was added p-toluenesulfonic acid monohydrate (0.056 g, 0.30 mmol). After stirring at rt for 24 h, the reaction mixture was cooled to 0 °C and the reaction was quenched by the slow addition of sat. $NaHCO_3$ (aq., 2.0 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 10 mL), dried (Na_2SO_4), and concentrated. The crude product was used directly without further purification.

The crude alcohol was taken up in CH_2Cl_2 (3.0 mL) and reacted with 4Å MS (20 mg), NMO (29 mg, 0.25 mmol) and TPAP (ca. 3.0 mg). After stirring at rt for 2 h, the reaction was concentrated to give 22 mg (65% for two steps) of **1.224** as a colorless oil. R_f 0.60 (hexanes:ethyl acetate, 3:1); $[\alpha]_D^{20}$ = +6.0 (*c* = 0.10, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 7.43 (d, *J* = 7.3 Hz, 2 H), 7.28-7.24 (m, 4 H), 7.20-7.05 (m, 9 H), 5.02 (d, *J* = 11.7, Hz, 1 H), 4.98 (d, *J* = 11.2 Hz, 1 H), 4.75 (d, *J* = 11.7 Hz, 1 H), 4.59 (d, *J* = 11.2 Hz, 1 H), 4.41 (d, *J* = 12.2 Hz, 1 H), 4.34 (d, *J* = 12.2 Hz, 1 H), 3.80-3.72 (m, 2 H), 3.65-3.64 (m, 2 H), 3.54 (t, *J* = 9.3 Hz, 1 H), 3.34 (ddd, *J* = 5.9, 3.4 Hz, 1 H), 3.22 (s, 3 H), 3.02 (ddd, *J* = 11.2, 9.8, 5.9 Hz, 1 H), 2.76 (dd, *J* = 16.6, 5.9 Hz, 1 H), 2.64 (d, *J* = 14.7 Hz, 1 H), 2.57 (dd, *J* = 17.1, 11.7 Hz, 1 H), 2.29 (d, *J* = 14.6 Hz, 1 H), 1.39 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 205.7, 169.6, 139.7, 139.3, 138.8, 128.6, 128.5, 128.4, 128.3, 127.9, 127.8, 127.7, 127.6, 84.7, 81.1, 79.6, 77.8, 77.0, 75.0, 73.6, 73.4, 69.5, 51.4, 42.5, 41.3, 24.6; IR (neat) 3030, 2917,2869, 1738, 1497, 1356, 1212, 1103, 1065, 752 cm^{-1}; LRMS (ESI) calcd for $C_{34}H_{38}O_8Na$ 597.3 ($M+Na^+$), found 597.2.



1. 224

Summary of COSY spectrum for **1.224**:

Proton at 2.29 ppm (H-8) shows crosspeak with proton at 2.64 ppm (H-8')

Proton at 2.57 ppm (H-6') shows crosspeaks with protons at 2.76 ppm (H-6) and 3.02 ppm (H-5)

Proton at 2.76 ppm (H-6) shows crosspeaks with protons at 2.57 ppm (H-6') and 3.02 ppm (H-5)

Proton at 3.02 ppm (H-5) shows crosspeaks with protons at 2.76 ppm (H-6),2.57 ppm (H-6') and 3.78 (H-4)

Proton at 3.78 ppm (H-4) shows crosspeaks with protons at 3.02 ppm (H-5) and 3.54 ppm (H-3)

Proton at 3.54 ppm (H-3) shows crosspeaks with protons at 3.78 ppm (H-4) and 3.74 ppm (H-2)

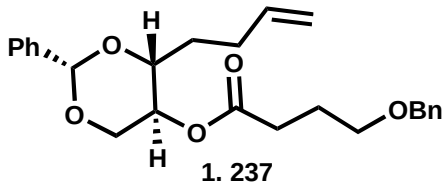
Proton at 3.34 ppm (H-1) shows crosspeaks with protons at 3.65 ppm (H-7) and 3.72 ppm (H-2)

Summary of 1D nOe difference experiments for **1.224**:

Irradiation at 2.29 ppm (H-8) resulted in enhancement at 3.78 ppm (H-4), 2.64 ppm (H-8') and 3.22 ppm (OMe)

Irradiation at 2.64 ppm (H-8') resulted in enhancement at 3.78 ppm (H-4), 2.29 ppm (H-8) and 3.22 ppm (OMe)

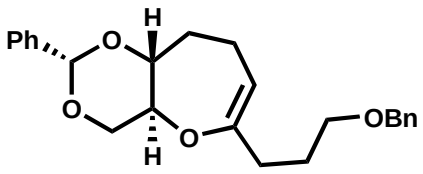
Irradiation at 3.54 ppm (H-1) resulted in enhancement at 3.54 ppm (H-3), 3.02 ppm (H-5) and 3.65 ppm (H-7)



1. 237

(4R,5S)-4-(but-3-enyl)-2-phenyl-1,3-dioxan-5-yl-4-(benzyloxy)butanoat (1.237)

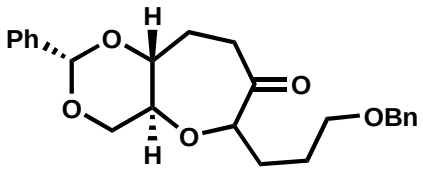
To a solution of **1.132** (1.01 g, 4.27 mmol) in CH_2Cl_2 (20.0 mL) at rt was added acid **1.236** (1.24 g, 6.39 mmol) followed by 1,3-dicyclohexylcarbodiimide (1.58 g, 7.67 mmol) and DMAP (0.78 g, 6.4 mmol). After stirring at rt for 12 h, the reaction mixture was filtered. The filtrate was washed with sat. $NaHCO_3$ (aq., 10 mL). The phases were separated. The aqueous phase was extracted with CH_2Cl_2 (5 x 50 mL) and dried with Na_2SO_4. Concentration and chromatography (hexanes:ethyl acetate, 10:1 to 5:1) provided **1.237** (1.51 g, 86%) as a colorless oil. R_f 0.55 (hexanes:ethyl acetate, 3:1); $[\alpha]_D^{20}$ = +16.3 (*c* = 0.258, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.60 (d, *J* = 7.3 Hz, 2 H), 7.24 (d, *J* = 7.3 Hz, 2 H), 7.20-7.07 (m, 6 H), 5.73 (dddd, *J* = 17.1, 10.3, 6.8, 6.8 Hz, 1 H), 5.29 (s, 1 H), 5.04-4.94 (m, 3 H), 4.36 (dd, *J* = 10.3, 4.89 Hz, 1 H), 4.24 (s, 2 H), 3.58 (dt, *J* = 9.3, 2.4 Hz, 1 H), 3.33 (t, *J* = 10.3 Hz,1 H), 3.19 (t, *J* = 5.9 Hz, 2 H), 2.34-2.26 (m, 1 H), 2.11 (t, *J* = 6.83 Hz,2 H), 2.18-2.10 (m, 1 H), 1.79-1.72 (m, 3 H), 1.66-1.59 (m, 1 H); ^{13}C NMR (125 MHz, C_6D_6) δ 171.7, 138.7, 138.3, 138.0, 128.7, 128.3, 127.7, 127.5, 127.4, 126.4, 114.8, 101.1, 78.3, 72.7, 68.7, 68.0, 66.8, 31.1, 30.8, 28.9, 25.1; IR (neat) 2929, 2857, 1741, 1453, 1365, 1166, 1093, 1027 cm^{-1}; LRMS (ESI) calcd for $C_{25}H_{30}O_5Na$ 433.2 (M+Na$^+$), found 433.2.



1. 238

(4aS,9aR,Z)-6-(3-(benzyloxy)propyl)-2-phenyl-4a,8,9,9a-tetrahydro-4H-[1,3]-dioxino[5,4-b]oxepine (1.238). To a solution of $TiCl_4$ (8.0 mL, 73 mmol) in CH_2Cl_2 (650 mL) at 0 ^oC was added THF (38.3 mL, 436 mmol) dropwise. The solution was stirred at 0 ^oC for 0.2 h and then TMEDA (65.5 mL, 436 mmol) was added dropwise to the light-yellow solution. The ice bath was removed and after 45 min Zn dust (10.7 g, 164 mmol) was added followed by $PbCl_2$ (2.4 g, 8.6 mmol). Over 20 min, the color of the reaction slurry turned from green to blue to blue-green at which time a solution of **1.237** (1.40 g, 3.41 mmol), CH_3CHBr_2 (6.60 ml, 96.0 mmol), and CH_2Cl_2 (50 mL) was added via a cannula. The resulting mixture was stirred rapidly and heated at reflux for 3 h. Then the reaction mixture was cooled to 0 ^oC and stirred with sat. K_2CO_3 (aq., 20 mL) for 1 h. The mixture was filtered and the residue was washed with 1:1 hexanes:ethyl acetate (3 x 100 mL). The filtrate was combined and concentrated. Flash chromatography (hexanes:ethyl acetate, 10:1 w/ 1% Et_3N) provided cyclic enol ether **1.238** (856 mg, 66%) as a colorless oil. R_f 0.63 (hexanes:ethyl acetate, 3:1); $[\alpha]_D^{20}$ = -9.5 (*c* = 0.42, THF); ^1H NMR (500 MHz, C_6D_6) δ 7.59 (d, *J* = 7.8 Hz, 2 H), 7.22 (d, *J* = 7.8 Hz, 2 H), 7.15-7.02 (m, 6 H), 5.29 (s, 1 H), 4.65 (dd, *J* = 8.3, 4.2 Hz, 1 H), 4.25 (s, 2 H), 4.20 (dd, *J* = 10.8, 5.1 Hz, 1 H), 3.5 (t, *J* = 10.6 Hz, 1 H), 3.46-3.32 (m, 2 H), 3.22 (t, *J* = 6.2 Hz, 2 H), 2.10-1.97 (m, 2 H), 1.92-1.84 (m, 2 H), 1.77-1.58 (m, 3 H), 1.49-1.38 (m, 1 H); ^{13}C NMR (125 MHz, C_6D_6) δ 159.3, 139.4, 138.8, 128.9, 128.5, 127.6, 126.8, 108.1, 101.1, 82.9, 75.4, 73.0,

69.6, 69.3, 32.7, 32.6, 27.5, 21.2; IR (neat) 2933, 2854, 1453, 1094 cm^{-1}; LRMS (ESI) calcd for $C_{24}H_{28}O_4Na$ 403.2 ($M+Na^+$), found 403.1.

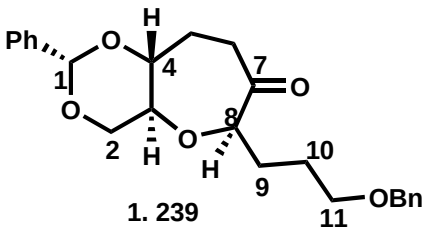


1. 239

(4aS,6R,9aR)-6-(3-(benzyloxy)propyl)-2-phenyl-tetrahydro-6H-[1,3]dioxino-[5,4-b]oxepin-7(8H)-one (1.239). To **1.238**(100 mg, 0.263 mmol) in CH_2Cl_2 (20 mL) at –78°C was added dimethyl dioxirane (2.0 mL of a 0.2 M solution in CH_2Cl_2, 0.4 mmol) dropwise. The reaction was warmed to 0 °C and concentrated. The colorless oil was taken up in CH_2Cl_2 (20 mL), cooled to -78 °C and *i*Bu_2AlH (0.53 mL of a 1.0 M solution in CH_2Cl_2, 0.53 mmol) was added at once. After stirring at -78 °C for 10 min, the reaction mixture was warmed up to 0 °C over 1 h. The reaction was quenched with sat. NH_4Cl (aq., 5 mL). The phases were separated. The aqueous phase was extracted with CH_2Cl_2 (5 x 100 mL) and dried with Na_2SO_4. Concentration and chromatography (hexanes:ethyl acetate, 5:1 to 3:1) provided the secondary alcohol (79 mg, 75%) as a colorless oil.

To the secondary alcohol from above (105 mg, 0.263 mmol) in CH_2Cl_2 (10.0 mL) at rt was added 4Å MS (100 mg), NMO (53 mg, 0.52 mmol), then TPAP (ca. 2.0 mg). After stirring at rt for 2 h, the reaction mixture was filtered through neutralized silica. Concentration and chromatography (hexanes:ethyl acetate, 10:1 to 4:1) provided ketone **1.239** (87.0 mg, 83%) as a colorless oil. R_f 0.40 (hexane:ethyl acetate, 3:1); $[\alpha]_D^{20}$ = +32.7 (*c* = 0.15, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.61 (d, *J* = 7.8 Hz, 2 H), 7.28 (d, *J* = 7.8 Hz, 2 H), 7.22-7.09 (m, 6 H), 5.27 (s, 1 H), 4.28 (s, 2 H), 4.02 (dd, *J* = 10.8, 5.5, 1 H), 3.54 (dd, *J* = 7.7, 4.9 Hz, 1 H), 3.39 (t, *J* = 10.0 Hz, 1 H), 3.29-3.20 (m, 3 H), 2.85

(ddd, *J* = 9.5, 5.3 Hz, 1 H), 2.42 (ddd, *J* = 14.1, 12.2,2.6 Hz, 1 H), 2.10 (dddd, *J* = 6.8, 1.8 Hz, 1 H), 1.85-1.78 (m, 1 H), 1.73-1.57 (m, 4 H), 1.54-1.44 (m, 1 H); ^{13}C NMR (125 MHz, C_6D_6) δ 213.3, 139.2, 138.6 129.0, 128.6, 128.3, 127.7,127.7, 126.7, 101.2, 87.1, 81.0, 76.0, 73.0, 69.8, 69.2, 36.2, 30.0, 29.5, 26.0; IR (neat) 2925, 2856, 1713, 1453, 1107 cm^{-1}; LRMS (ESI) calcd for $C_{24}H_{28}O_5Na$ 419.2 ($M+Na^+$), found 419.2.



1. 239

Summary of COSY spectrum for **1.239**:

Proton at 4.02 ppm (H-2) shows crosspeaks with protons at 3.39 ppm (H-2) and 2.85 ppm (H-3)

Proton at 3.54 ppm (H-8) shows crosspeak with proton at 1.68 ppm (H-9)

Proton at 3.39 ppm (H-2) shows crosspeak with proton at 4.02 ppm (H-2)

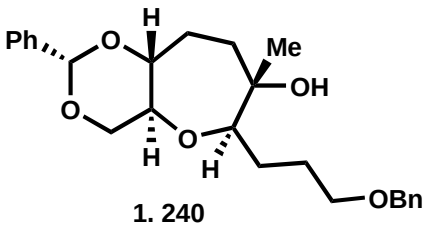
Proton at 3.26 ppm (H-10) shows crosspeak with proton at 1.68 ppm (H-9)

Proton at 2.85 ppm (H-3) shows crosspeaks with protons at 4.02 ppm (H-2), 3.39 ppm (H-2) and 3.26 ppm (C-4)

Summary of 1D NOE difference experiments for **1.239**:

Irradiation at 2.85 ppm (H-3) resulted in enhancement at 3.54 ppm (H-8)

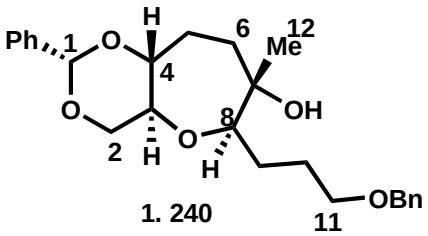
Irradiation at 3.54 ppm (H-8) resulted in enhancement at 2.85 ppm (H-3)



1. 240

(4aS,6R,7S,9aR)-6-(3-(benzyloxy)propyl)-7-methyl-2-phenyl-hexahydro-4H-[1,3] dioxino[5,4-b]oxepin-7-ol (1.240). To a solution of **1.239** (40.0 mg, 0.101 mmol) in toluene (4.0 mL) at -78 ^{o}C was added MeMgBr (0.13 mL of a 3.0 M solution in ether, 0.39 mmol). After stirring at -78 ^{o}C for 10 min, the reaction mixture was warmed up to 0 ^{o}C and kept at this temperature for 0.5 h. The reaction was quenched with sat. NH_4Cl (aq., 5 mL). The aqueous phase was extracted with CH_2Cl_2 (5 x 20 mL) and dried with Na_2SO_4. Concentration and chromatography (hexanes:ethyl acetate, 5:1 to 3:1) provided **1.240** (35 mg, 84%) and **epi-1.240** (5.0 mg, 12%) as colorless oils.

Data for **1.240**: R_f 0.18 (hexanes:ethyl acetate, 3:1); $[\alpha]_D^{20}$ = +13.0 (*c* = 0.115, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.67 (dd, *J* = 8.3, 1.5 Hz, 2 H), 7.32 (d, *J* = 6.8 Hz, 2 H), 7.26-7.09 (m, 6 H), 5.31 (s, 1 H), 4.34 (s, 2 H), 4.23 (dd, *J* = 10.3, 4.4 Hz, 1 H), 3.41 (t, *J* = 9.9 Hz, 1 H), 3.37-3.19 (m, 3 H), 3.13 (dd, *J* = 10.3, 1.5 Hz, 1 H), 1.88-1.74 (m, 3 H), 1.69-1.62 (m, 1 H), 1.59-1.51 (m, 2 H), 1.48-1.29 (m, 2 H), 0.93 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ139.4, 138.9, 128.8, 128.5, 127.6, 126.8, 101.5, 88.8, 83.2, 77.2, 74.3, 73.0, 70.5, 70.0, 39.4, 27.9, 27.7, 27.5, 23.9; IR (neat) 3454, 2932, 2858, 1453, 1366, 1099 cm^{-1}; LRMS (ESI) calcd for $C_{25}H_{32}O_5Na$ 435.2 (M+Na$^+$), found 435.2.



1. 240

Summary of COSY spectrum for **1.240**:

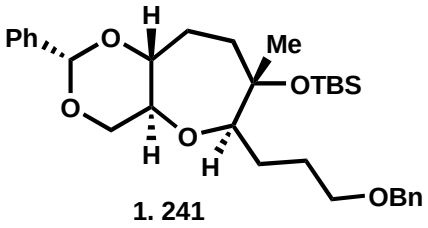
Proton at 4.23 ppm (H-2) shows crosspeak with proton at 3.41 ppm (H-2)

Proton at 3.41 ppm (H-2) shows crosspeaks with protons at 3.30 ppm (H-3) and 4.23 ppm (H-2)

Proton at 3.13 ppm (H-8) shows crosspeak with proton at 1.40 ppm (H-9)

Summary of 1D NOE difference experiments for **1.240**:

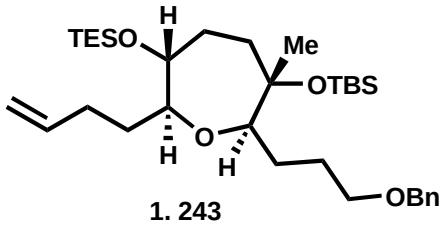
Irradiation at 0.92 ppm (CH_3-12) resulted in enhancement at 1.60 ppm (H-6) and 1.75 ppm (H-5)



1. 241

((4aS,6R,7S,9aR)-6-(3-(benzyloxy)propyl)-7-methyl-2-phenyl-hexahydro-4H-[1,3] dioxino[5,4-b]oxepin-7-yloxy)(tert-butyl)dimethylsilane (1.241). To the solution of **1.240** (100 mg, 0.242mmol) in CH_2Cl_2 (10.0 mL) at 0 ^oC was added NEt_3 (0.610 mL, 4.36 mmol) followed by TBSOTf (0.560 mL, 2.44 mmol) and DMAP (6.0 mg, 0.050 mmol). The reaction mixture was warmed to rt over 1 h at kept at this temperature for 1 h. The reaction was quenched with sat. $NaHCO_3$ (aq., 5 mL). The aqueous phase was extracted with CH_2Cl_2 (5 x 50 mL) and dried with Na_2SO_4. Concentration and chromatography (hexane/EtOAc, 50:1 to 10:1) provided the protected alcohol **1.241** (117 mg, 92%) as a colorless oil. R_f 0.83 (hexanes:ethyl acetate, 3:1); $[\alpha]_D^{20}$ = +8.0 (*c* = 0.2, THF); ^1H NMR (500 MHz, C_6D_6) δ 7.68 (dd, *J* = 7.3, 1.5 Hz, 2 H), 7.32 (d, *J* = 7.3 Hz, 2 H), 7.23-7.09 (m, 6 H), 5.33 (s, 1 H), 4.34 (d, *J* = 3.42 Hz, 2 H), 4.26 (dd, *J* = 10.3, 4.4

Hz, 1 H), 3.49 (t, *J* = 9.8 Hz, 1 H), 3.43-3.33 (m, 3 H), 3.31-3.25 (m, 2 H), 2.03-1.96 (m, 1 H), 1.92-1.79 (m, 4 H), 1.68-1.55 (m, 2 H), 1.46-1.40 (m, 1 H), 1.06 (s, 3 H), 0.94 (s, 9 H), 0.051 (d, *J* =1.5 Hz, 6 H); ^{13}C NMR (125 MHz, C_6D_6) δ 139.4, 139.0, 128.8, 128.5,128.3, 127.7, 127.7, 127.5, 126.8, 101.5, 89.7, 83.4, 77.9, 77.8, 72.9, 70.5, 70.0, 39.4, 27.9, 27.7, 27.6,26.0, 25.9, 24.0, 18.3, -2.0, -2.1; IR (neat) 2953, 2856, 1462, 1361, 1255, 1102 cm^{-1}; LRMS (ESI) calcd for $C_{31}H_{46}O_5SiNa$ 549.3 ($M+Na^+$), found 549.2.



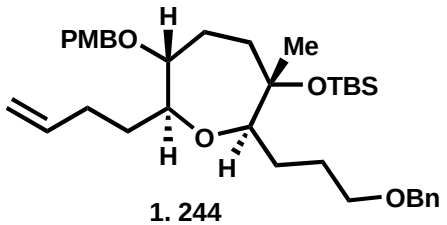
1. 243

(2R,3S,6R,7S)-2-(3-(benzylox)propyl)-7-(but-3-enyl)-3-(tert-butyldimethylsil-yloxy)-3-methyl-6-(triethylsilyloxy)oxepane (1.243). To a solution of **1.241** (65 mg, 0.12 mmol) in MeOH (10.0 mL) at rt was added PPTS (34 mg, 0.14mmol). After heating to reflux for 3 h, the reaction mixture was cooled to rt and the reaction was quenched with sat. $NaHCO_3$ (aq., 5 mL). The aqueous phase was extracted with CH_2Cl_2 (5 x 50 mL) and dried with Na_2SO_4. Concentration and chromatography (MeOH:CH_2Cl_2, 1:6) provided diol **1.242** (50.0 mg, 93 %) as a colorless oil.

To a solution of the diol **1.242** (50.0 mg, 0.114 mmol) from above in CH_2Cl_2 (5.0 mL) at -78 ^{o}C was added 2,6-lutidine (27 μL, 0.23 mmol) followed by Tf_2O (20 μL, 0.12 mmol). After 15 min, TESOTf (0.270 mL, 2.32 mmol) and 2,6-lutidine (0.260 mL, 1.15 mmol) was added and the reaction mixture was warmed to rt. After 0.5 h, the reaction mixture was cooled to -78 ^{o}C and the reaction was quenched with sat. $NaHCO_3$ (aq., 6.0 mL). The aqueous phase was extracted with CH_2Cl_2 (5 x 50 mL), dried with Na_2SO_4 and

concentrated. The yellow oil was passed through a short plug of silica (hexanes:ethyl acetate, 5:1) and immediately taken on to the next step.

To a solution of the triflate from above in THF (5.0 mL) at -40 °C was added *via* cannula to a solution of allyl cuprate [Prepared from allyl magnesium chloride (1.3 mL of a 2.0 M solution in THF, 2.6 mmol) and CuI (280 mg, 1.47 mmol) at -78 °C. The reaction mixture was slowly warmed to 0 °C and stirred for 1 h]. The reaction mixture was stirred at -40 °C for 2 h, warmed to rt and quenched with sat. NH_4Cl (aq., 10 mL). The aqueous phase was extracted with CH_2Cl_2 (5 x 50 mL) and dried with Na_2SO_4. Concentration and chromatography (hexanes:ethyl acetate, 5:1 to 3:1) provided protected alcohol **1.243** (49.0 mg, 74% for two steps) as a colorless oil. R_f 0.90 (hexanes:ethyl acetate, 5:1); ^{1}H NMR (500 MHz, C_6D_6) δ 7.34-7.31 (m, 2 H), 7.22-7.07(m, 3 H), 5.90 (dddd, *J* = 16.9, 10.2, 6.5 Hz, 1 H), 5.14 (dd, *J* = 17.2, 1.7 Hz, 1 H), 5.01 (dd, *J* = 10.4, 1.5 Hz,1 H), 4.34 (s, 2 H), 3.52-3.39 (m, 5 H), 2.55-2.43 (m, 1 H), 2.35-2.16 (m, 1 H), 2.07-1.50 (m, 10 H), 1.20 (s, 3 H), 1.02-0.97 (s, 18 H), 0.58 (q, *J* = 7.82 Hz, 6 H), 0.18 (d, *J* = 2.34 Hz, 6 H); ^{13}C NMR (125 MHz, C_6D_6) δ 139.1, 128.4, 128.3, 127.7, 127.6, 127.5, 127.4, 114.7, 87.3, 86.9, 77.7, 77.2, 72.8, 70.7, 37.5, 34.8, 30.7, 29.7, 28.0, 27.7, 26.1, 23.5, 18.3, 7.2, 5.5, -1.9, -2.0; IR (neat) 2954, 2933, 1461, 1254, 1100 cm^{-1}; LRMS (ESI) calcd for $C_{33}H_{60}O_4Si_2Na$ 599.4 ($M+Na^+$), found 599.3.

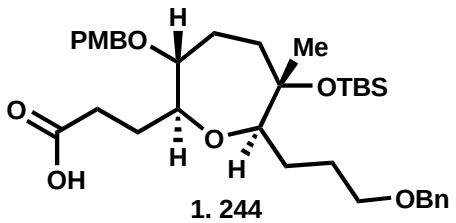


1. 244

((2R,3S,6R,7S)-6-(4-methoxybenzyloxy)-2-(3-(benzyloxy)propyl)-7-(but-3-en-yl)-3-methyloxepan-3-yloxy)(tert-butyl)dimethylsilane (1.244). To a solution of **1.243**

(20. mg, 0.035 mmol) in MeOH (4.0 mL) at 0 °C was added 10-camphorsulfonic acid (8.0 mg, 0.035 mmol).The reaction mixture was warmed to rt over 1 h. The reaction was quenched with sat. $NaHCO_3$ (aq., 2.5 mL). The aqueous phase was extracted with CH_2Cl_2 (5 x 50 mL) and dried with Na_2SO_4. Concentration and chromatography (hexanes:ethyl acetate, 10:1 to 3:1) provided the free alcohol (16 mg, 100%) as a colorless oil.

To the free alcohol (10. mg, 0.022 mmol) from above in THF (4.0 mL) was added KH (5.0 mg of a 30 wt% solution in mineral oil, 0.038 mmol) at 0 °C. The reaction mixture was warmed up to rt and stirred at rt for 1 h. The reaction mixture was cooled to 0 °C and PMBBr (4.0 μL, 0.031 mmol) was added. The reaction mixture was warmed up to rt and stirred at rt for 5 h. The reaction was quenched with sat. NH_4Cl (aq., 1.0 mL). The aqueous phase was extracted with CH_2Cl_2 (5 x 50 mL) and dried with Na_2SO_4. Concentration and chromatography (hexanes:ethyl acetate, 10:1) provided protected alcohol **1.244** (11 mg, 87%) as a colorless oil. R_f 0.80 (hexanes:ethyl acetate, 3:1); $[\alpha]_D^{20}$ = +8.0 (*c* = 0.014, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.33-7.31 (m, 2 H), 7.23-7.09 (m, 5 H), 6.81 (d, *J* = 8.8 Hz, 2 H), 5.85 (dddd, *J* = 16.7, 10.1, 6.4 Hz, 1 H), 5.09 (dd, *J* = 17.2, 2.0 Hz, 1 H), 5.0-4.98 (m, 1 H), 4.40 (d, *J* = 11.4 Hz, 1 H), 4.34 (s, 2 H), 4.17 (d, *J* = 11.4 Hz, 1 H), 3.58-3.54 (m, 1 H), 3.49-3.39 (m, 3 H), 3.29 (s, 3 H), 3.22-3.18 (m, 1 H), 2.44-2.37 (m, 1 H), 2.26-2.14 (m, 1 H), 2.07-1.93 (m, 3 H), 1.89-1.57 (m, 7 H), 1.22 (s, 3 H), 0.97 (s, 9 H), 0.13 (d, *J* = 1.8 Hz, 6 H); ^{13}C NMR (125 MHz, C_6D_6) δ 158.5, 139.0, 134.0, 130.2, 130.1, 129.7, 129.4, 128.4, 128.3, 127.6, 127.4, 114.7, 114.1, 114.0, 87.3, 85.1, 83.2, 77.6, 72.8, 71.6, 70.7, 54.7, 37.6, 37.5, 35.0, 30.7, 30.2, 27.9, 27.6, 26.1, 24.4, 23.0, 18.3, -1.8, -1.9; IR (neat) 2928, 1612, 1512, 1247 cm^{-1}; LRMS (ESI) calcd for $C_{35}H_{54}O_5SiNa$ 605.4 (M+Na$^+$), found 605.3.



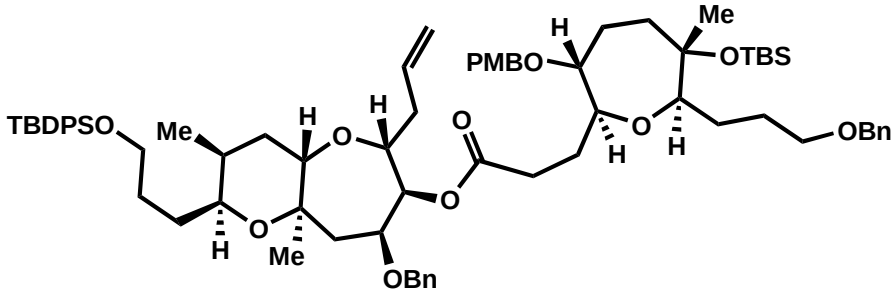
1. 244

3-((2S,3R,6S,7R)-3-(4-methoxybenzyloxy)-7-(3-(benzyloxy)propyl)-6-(tertbutyldimethylsilyloxy)-6-methyloxepan-2-yl)propanoic acid (1.245). To a solution of **1.244** (10. mg, 0.017 mmol), THF: *t*BuOH: H_2O (5:5:1, 1 mL), N-methylmorpholine N-oxide (2.1 mg, 0.021 mmol) was added OsO_4 (10.3 μL of a 0.16 M solution in H_2O, 0.0016 mmol) at rt. The reaction mixture was stirred at rt for 16 h. Sodium bisulfite (0.2 g) was added to the reaction mixture. After stirring at rt for 2 h, the reaction was diluted with H_2O and the aqueous phase was extracted with CH_2Cl_2 (5 x 20 mL). The organic extracts were dried with Na_2SO_4 and concentrated. The resulting oil was passed through a plug of silica gel and used in the next step without further purification.

To a solution of the diol from above in benzene (2.0 mL) was added $Pb(OAc)_4$ (9.4 mg, 0.021 mmol) at rt. After 1 h at rt, the reaction mixture was passed through a plug of silica gel, concentrated and used in the next step.

To a solution of the aldehyde from above in *t*BuOH (0.5 mL) at rt was added 2-methyl-2-butene (0.30 mL, 2.8 mmol). A solution of $NaClO_2$ (9.0 mg, 0.10 mmol) with NaH_2PO_4 (16 mg, 0.13 mmol) in H_2O (0.5 mL) was added dropwise. After stirring rapidly at rt for 3 h, the reaction was quenched with sat. NH_4Cl (aq., 1.0 mL). The aqueous phase was extracted with CH_2Cl_2 (5 x 50 mL) and dried with Na_2SO_4. Concentration and chromatography (hexanes:ethyl actate, 10:1 to 2:1) provided acid **1.245** (5.6 mg, 54% for three steps) as a colorless oil. R_f 0.15 (hexanes:ethyl actate, 1:1); $[\alpha]_D^{20}$ = -0.13 (*c* = 0.12, benzene); ^{1}H NMR (500 MHz, C_6D_6) δ 7.34 (d, *J* = 7.5 Hz, 2

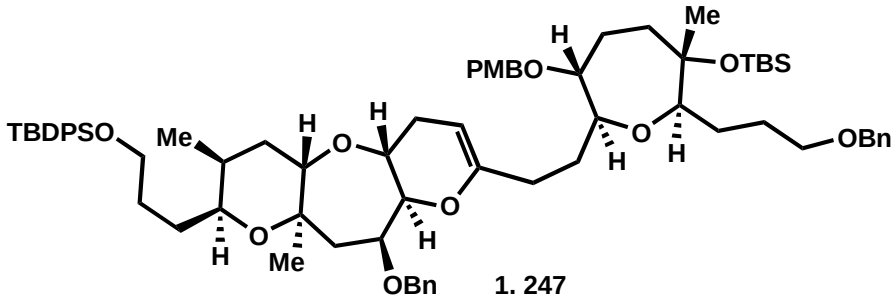
H), 7.24-7.08 (m, 5 H), 6.82 (d, *J* = 8.5 Hz, 2 H), 4.37-4.32 (m, 3 H), 4.14 (d, *J* = 11.2 Hz, 1 H), 3.451-3.47 (m, 1 H), 3.43-3.36 (m, 3 H), 3.31 (s, 3 H), 3.12-3.08 (m, 1 H), 2.53-2.47 (m, 1 H), 2.39-2.33 (m, 1 H), 2.0-1.90 (m, 4 H), 1.81-1.74 (m, 2 H), 1.68-1.59 (m, 2 H), 1.55-1.46 (m, 2 H), 1.18 (s, 3 H), 0.97 (s, 9 H), 0.11 (s, 6 H); ^{13}C NMR (125 MHz, C_6D_6) δ 179.1, 159.7, 139.5, 131.0, 129.5, 128.5, 128.3,127.7, 127.4, 114.1, 87.1, 84.5, 82.7, 77.5, 72.8, 70.6, 54.7, 37.4, 30.4, 30.2, 27.8, 27.5, 26.1, 24.3, 23.0, 18.3, -1.8, -1.9; IR (neat) 3500, 2854, 1709, 1513, 1250, 1105 cm^{-1}; LRMS (ESI) calcd for $C_{34}H_{51}O_7Si$ 599.3 (M-H$^+$), found 599.4.



1. 246

(2S,3S,4aS,6R,7S,8S,9aR)-6-allyl-8-(benzyloxy)-2-(3-(tert-butyldiphenylsilyl-oxy)propyl)-3,9a-dimethyl-octahydro-2H-pyrano[3,2-b]oxepin-7-yl 3-((2S,3R,6S,7R) -7-(3-(4-methoxybenzyloxy)propyl)-6-(tert-butyldimethylsilyloxy)-6-methyl-3-(triet-hylsilyloxy)oxepan-2-yl)propanoate (1.246). To a solution of **1.245** (9.0 mg, 0.015 mmol) in THF (1.0 mL) was added NEt_3 (16. μL, 0.12 mmol), and 2,4,6-trichlorobenzoyl chloride (14 μL, 0.090 mmol). After stirring at 40 ^{o}C for 2 h, the mixture was concentrated under reduce pressure. A solution of **1.171** (8.6 mg, 0.014 mmol), DMAP (20. mg, 0.18 mmol) and toluene (1.0 mL) was added at room temperature. A white solid precipitated out of solution immediately. The reaction mixture was stirred at 40 ^{o}C overnight. The reaction was quenched with sat. $NaHCO_3$ (aq., 3 mL). The aqueous phase

was extracted with CH_2Cl_2 (5 x 10 mL). The organic extracts were dried with Na_2SO_4. Concentration and chromatography (hexanes:ethyl actate 20:1 to 10:1) provided ester **1.246** (12.6 mg, 77%) as a colorless oil. R_f 0.78 (hexanes:ethyl actate, 3:1); $[\alpha]_D^{20}$ = -16.5 (*c* = 0. 2, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 7.79 (d, *J* = 3.4 Hz, 4 H), 7.36-7.06 (m, 18 H), 6.85 (d, *J* = 8.3 Hz, 2 H), 5.98-5.90 (m, 1 H), 5.64 (s, 1 H), 5.09-5.01 (m, 2 H), 4.50 (d, *J* = 12.2 Hz, 1 H) 4.41-4.37 (m, 3 H), 4.20 (d, *J* = 11.2 Hz, 1 H), 3.84-3.69 (m, 5 H), 3.52-3.43 (m, 6 H), 3.31 (s, 3 H), 3.16 (br, 1 H), 2.68-2.59 (m, 2 H), 2.52-2.45 (m, 1 H), 2.35 (t, *J* = 6.3 Hz, 2 H), 2.09-1.89 (m, 6 H), 1.81-1.77 (m, 2 H), 1.68-1.59 (m, 4 H), 1.56-1.51 (m, 6 H), 1.37-1.31 (m, 3 H),1.18 (s, 12 H), 1.15 (s, 3 H), 0.97 (s, 9 H), 0.11 (s, 6 H); ^{13}C NMR (125 MHz, C_6D_6) δ172.6, 159.7, 139.7, 138.9, 136.0, 134.4, 131.1, 129.9, 129.6, 129.5, 128.6, 128.4, 128.3,128.2, 127.7, 127.6, 127.4, 117.7, 114.1 , 87.1, 84.6, 84.4, 82.8, 81.3, 77.5, 77.4, 74.2, 74.1, 73.9, 72.8, 70.8, 70.7, 70.6, 64.3, 54.8, 43.1, 39.6, 37.5, 34.5, 33.0, 31.4, 30.8, 29.8, 29.4, 27.9, 27.6, 27.2, 26.1, 24.4, 23.0, 19.5, 18.4, 16.4, 12.6, -1.79, -1.84; IR (neat) 2951, 2857, 1737, 1612, 1455, 1249, 1107 cm^{-1}; LRMS (ESI) calcd for $C_{74}H_{104}O_{11}Si_2Na$ 1247.7 ($M+Na^+$), found 1247.4.



1. 247

Enol ether ring 1.247. A flame-dried three-necked flask fitted with a condenser was cooled to 0 °C and charged with CH_2Cl_2 (9.3 mL) followed by $TiCl_4$ (0.113 mL, 1.03 mmol). To the resulting solution was added THF (0.550 mL, 6.27 mmol) dropwise at which time the solution turned yellow. The addition of THF was followed by the

dropwise addition of TMEDA (0.930 mL, 6.17 mmol), resulting in the formation of a brown solution. The ice bath was removed and the mixture was allowed to stir for 20 min. Activated Zn dust (151 mg, 2.32 mmol) and $PbCl_2$ (34.0 mg, 0.122 mmol) were then added. The resulting mixture went through a series of color changes from brown to green to purple and finally to blue-green over the course of 5 min. To the slurry was transferred a solution of ester **1.246** (10.0 mg, 8.16 μmol) and CH_3CHBr_2 (0.093 mL, 1.0 mmol) in CH_2Cl_2 (0.5 mL + 0.5 mL rinse) via cannula. The reaction mixture was then heated at reflux for 4 h. Following this time period the mixture was cooled to 0 °C and quenched with sat. K_2CO_3 (aq., 0.1 mL). After stirring for 30 min at 0 °C, the resulting mixture was filtered. The mixture was filtered and the residue was washed with 1:1 hexanes:ethyl acetate (3 x 10 mL). The filtrate was combined and concentrated. Chromatography (hexanes:ethyl acetate, 20:1 to 10:1) provided cyclic enol ether **1.247** (7.0 mg, 72%) as a colorless oil. R_f 0.85 (hexanes:ethyl acetate, 3:1); $[\alpha]_D^{20}$ = -18.3 (*c* = 0. 18, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 7.80-7.78 (m, 4 H), 7.46 (d, *J* =7.3 Hz, 1 H), 7.31 (d, *J* = 6.8 Hz, 2 H), 7.24-7.06 (m, 15 H), 6.81-6.79 (m, 2 H), 4.73-4.61 (m, 3 H), 4.46-4.45 (m, 1 H),4.41 (d, *J* =11.2 Hz, 1 H), 4.33 (s, 2 H), 4.25-4.18 (m, 2 H), 3.92 (m, 1 H), 3.74-3.61 (m, 3 H), 3.51-3.39 (m, 4 H), 3.35-3.30 (m, 2 H), 3.28 (s, 3 H), 2.58-2.54 (m, 1 H), 2.48-2.28 (m, 2 H), 2.24-2.19 (m, 1 H), 2.11-1.97 (m, 5 H), 1.94-1.82 (m, 2 H), 1.79-1.71 (m, 3 H), 1.69-1.47 (m, 8 H), 1.45-1.35 (m, 4 H), 1.22 (s, 3 H), 1.18 (s, 9H), 0.97 (s, 9 H), 0.91 (d, *J* = 6.8 Hz, 3 H), 0.12 (d, *J* =2.9 Hz, 6 H); ^{13}C NMR (125 MHz, C_6D_6) δ 159.7, 154.2, 139.7, 139.5, 136.0, 134.5, 131.2, 129.9, 129.4, 128.8, 128.4,128.3, 127.6, 127.5, 127.4, 127.2, 126.6, 125.4, 114.0, 93.2, 87.4, 85.4, 83.3, 81.5, 79.2, 77.7, 77.6, 72.8, 72.8, 72.2, 71.7, 71.4, 70.8, 70.7, 64.4, 54.7, 44.4, 37.6, 35.0, 33.5, 33.2, 30.8, 30.5, 30.2, 29.9,

29.5, 27.7, 27.2, 27.1, 26.1, 24.6, 23.1, 20.4, 19.5, 18.4, 12.8, 12.7, -1.7, -1.8; IR (neat) 2927, 2856, 1612, 1587, 1462, 1378, 1249, 1110, 834 cm^{-1}; LRMS (ESI) calcd for $C_{73}H_{102}O_{10}Si_2Na$ 1217.7 ($M+Na^+$), found 1217.5.

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CHAPTER 2

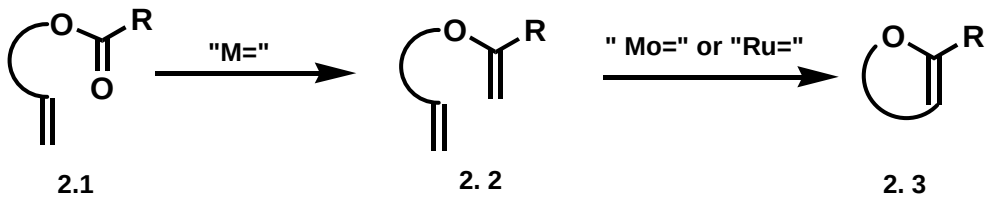
OLEFINIC AMIDE AND OLEFINIC LACTAM CYCLIZATIONS BY USING A REDUCED TITANIUM ALKYLIDENE

Introduction

Because enamides show a good balance between reactivity and stability, they are important in organic synthesis.[1]Thenucleophilic reactivity by the virtue of the enamine character is tempered by the electron withdrawing functionality upon the nitrogen center, leading to significant chemical stability. These two characteristics make enamides key intermediates in the synthesis of a variety of heterocyclic compunds.[1] The importance and relevance of enamides both as building blocks and target units has been reflected in the number of different approaches reported for their synthesis.[2] However, addition work is still needed. In particular, methods that utilize simple methods to accomplish their synthesis are needed.

Titanium reagents for the alkylidenation of carboxylic acid derivatives

Alkylidenation of esters as illustrated for **2.1** are very useful transformations. Ring closing metathesis of alkylidenated product **2.2** afford cyclic enol ether **2.3** which is a powerful intermediate in organic synthesis (Scheme 2.1).[3]



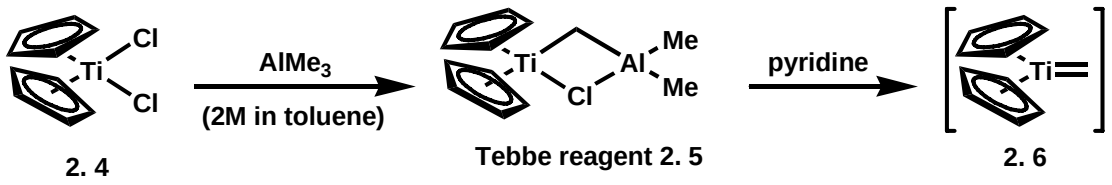
2.1 2. 2 2. 3

Scheme 2.1. A general way to synthesize cyclic enol ethers

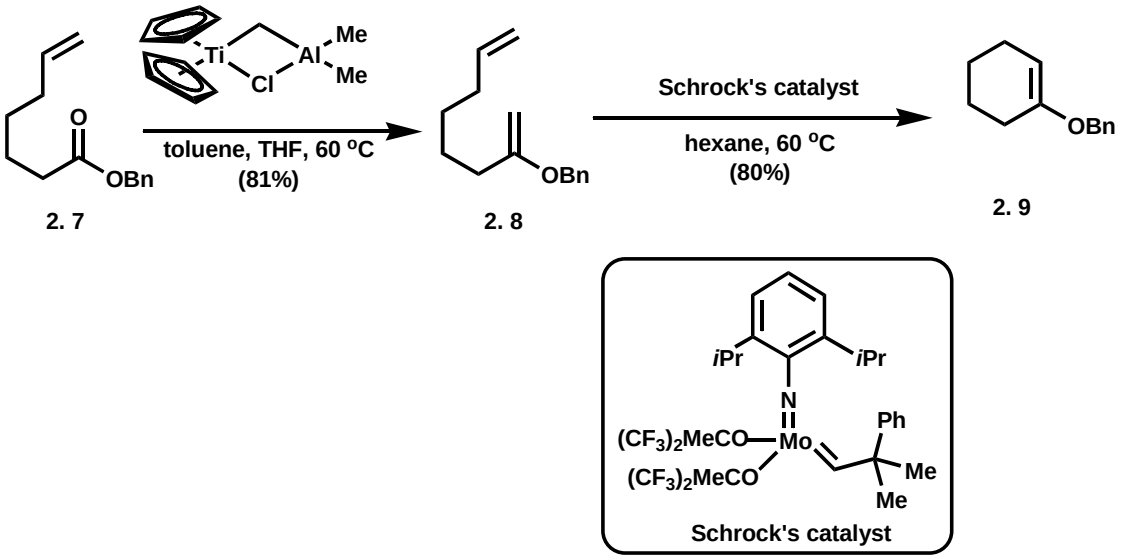
Titanium-based reagents have been used widely to alkylidenate carbonyl groups.[3,4] The methylenation of aldehyde and ketones by these non-basic, highlyreactive reagents provides advantages over other methylenation methods (such as the Wittig reaction), particularly when base-sensitive substrates are used or when the carbonyl group is sterically hindered.[3(a)] In addition,the alkylidenation of esters makes these titanium-based reagents distinct.[3(a)]

The Tebbe reagent **2.5** is a titanium-aluminum metallacycle which contains two tetrahedral centers linked by a pair of bridging ligands.[5,6] Titanium features two cyclopentadienyl ($[C_5H_5]^-$, or Cp) ligands and aluminum features two methyl ligands. The titanium and aluminum atoms in the Tebbe reagent are bridged by both CH_2 and chloride ligands. It is synthesized from titanocene dichloride and trimethylaluminum in toluene solution[6] (Scheme 2.2). Treatment of Tebbe reagent with a mild Lewis base such as pyridine affords a highly reactive titanocene methylidene **2.6** which is able to react with a wide range of carbonyl derivatives.[5, 7]

In 1994, Grubbs and co-workers reported the synthesis of furan and pyran rings by a two-step sequence involving Tebbe methylenation followed by ring closing metathesis (Scheme 2.3).[8]

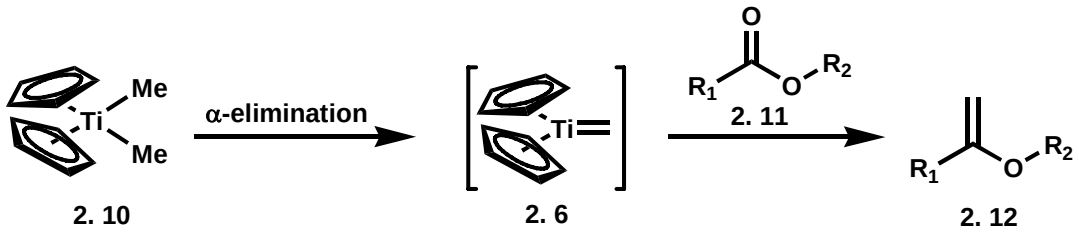


Scheme 2.2. Synthesis of the Tebbe reagent



Scheme 2.3. Synthesis of the cyclic enol ether by a two-step's protocol

Dimethyltitanocene **2.10**, also commonly called the Petasis reagent, is readily prepared by the reaction of methyl magnesium chloride[9] or methyllithium[10] with titanocene dichloride. Studies by Hughes[11] showed the methylenation of carbonyl groups by the Petasis reagent proceeds by rate-determining generation of titanocene methylidene **2.6** via α-elimination, followed by a rapid reaction with a carbonyl group (Scheme 2.4). The advantages of the Petasis reagent include its stability to air and moisture and its non-Lewis acidic nature. However, their diminished reactivity limits their utility.[3]

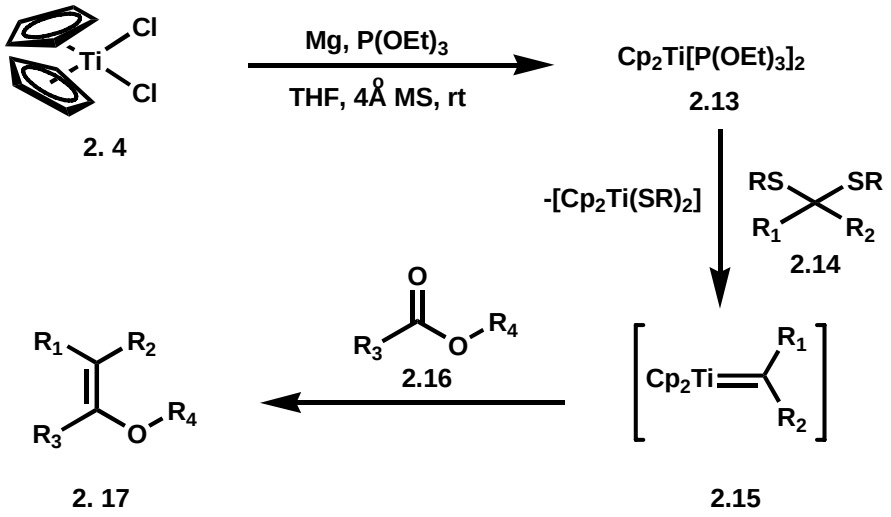


2. 10 2. 6 2. 12

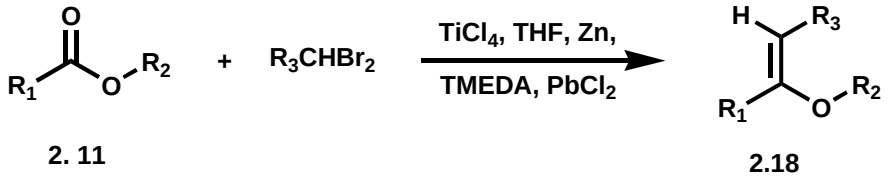
Scheme 2.4. Methylidenation by the Petasis reagent

The Takeda reagent,$Cp_2Ti[P(OEt)_3]_2$ **2.13**, is generated by reduction of titanocene dichloride with magnesium in the presence of triethylphosphite in dry THF (Scheme 2.5). In 1997, Takeda and co-workers reported the reduction of thioacetals by low valent titanium complex **2.13** to give titanium reagents **2.15** which would alkylidenate esters.[12] The key advantage of the Takeda reagent is the range of alkylidenating reagents than can be produced and the ease of synthesis of thioacetal substrates.[3(a)]

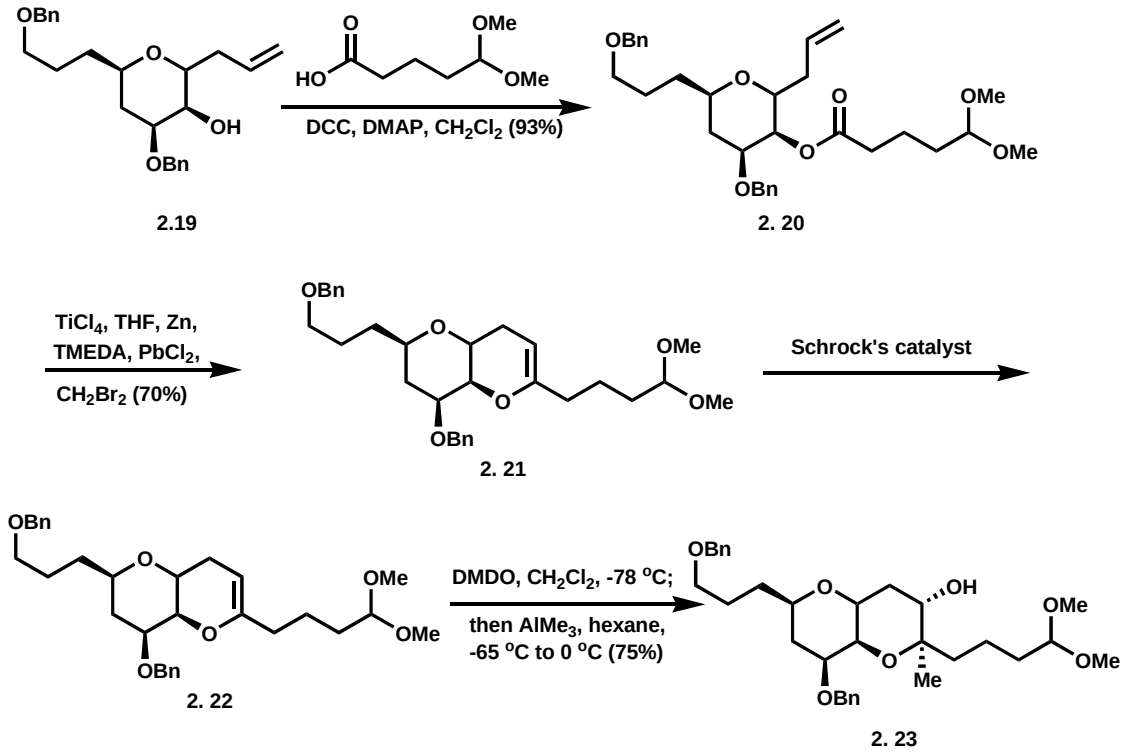
In 1987, Takai and co-workers reported the stereoselective alkylidenation of esters to give Z-enolethers[3(d)] (Scheme 2.6). A titanium alkylidene reagent prepared from $TiCl_4$, TMEDA, THF,1,1-dibromoalkane, Zn and $PbCl_2$ was used in these reactions. Rainier and co-workers developed a general synthetic strategy to polycyclic ethersthat involves a sequential esterification, a Takai methylenation, ring closing metathesis and C-glycoside formation.In the formal total synthesis of (±)-hemibrevetoxin B, alcohol **2.19** was esterified and subjected to methylenation followed by ring closing metathesis to give cyclic enol ether **2.21**. Epoxidation followed by trimethylaluminum addition gave **2.23** (Scheme 2.7).[13]



Scheme 2.5. Alkylidenation by the Takeda reagent

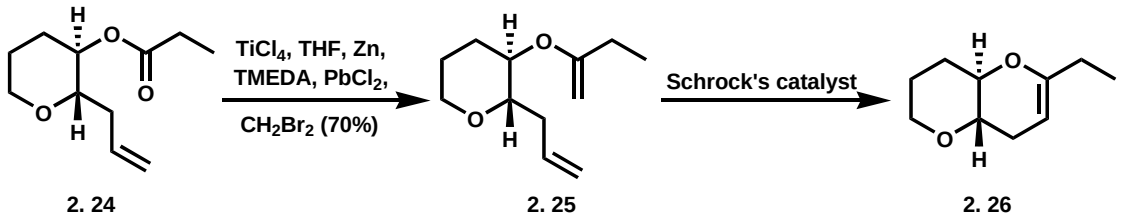


Scheme 2.6. Alkylidenation by the Takai reagent



Scheme 2.7. Rainier's strategy towards polycyclic enol ethers

Clark and co-workers reported a similar approach to construct cyclic enol ethers involving a Takai methylenation and ring closing metathesis (Scheme 2.8). They first converted olefinic-ester **2.24** to acyclic enol ether **2.25**. Then they used ring closing metathesis and Schrock's catalyst to generate cyclic enol ether **2.26**.[14]

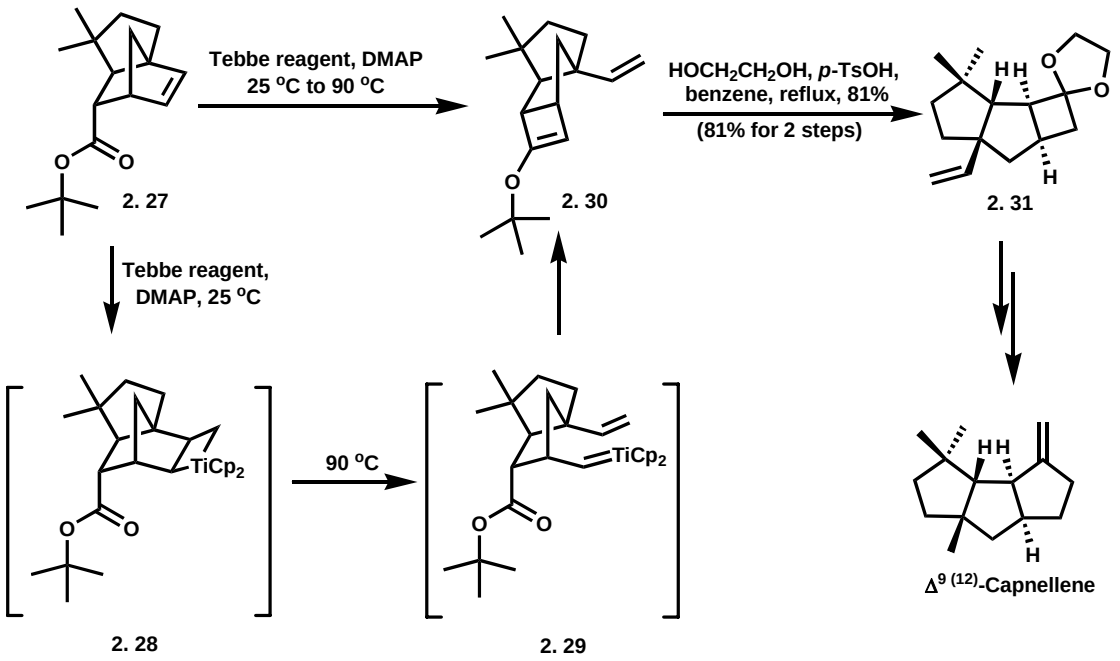


Scheme 2.8. Clark's two-step's protocol to construct cyclic enol ethers

Related work on one-step olefinic-ester cyclization

There are relatively few reports of transforming **2.1** into **2.3** bypassing acyclic enol ether **2.2** although it is more efficient than the two-step protocol. Here is a brief summary of the one-step olefinic-ester cyclization.

In the total synthesis of capnellene[15], Grubbs and co-workers found that ester-substituted norbornene **2.27** reacted with the Tebbe reagent to give stable metallacycle **2.28**. On heating, metallacycle **2.28** rearranged to a carbene-olefin complex **2.29**. An intramolecular trapping of the intermediate titanium alkylidene by tert-butyl ester afforded **2.30** which underwent hydrolysis and protection to give ketal **2.31** in 81% yield based on **2.27** (Scheme 2.9).



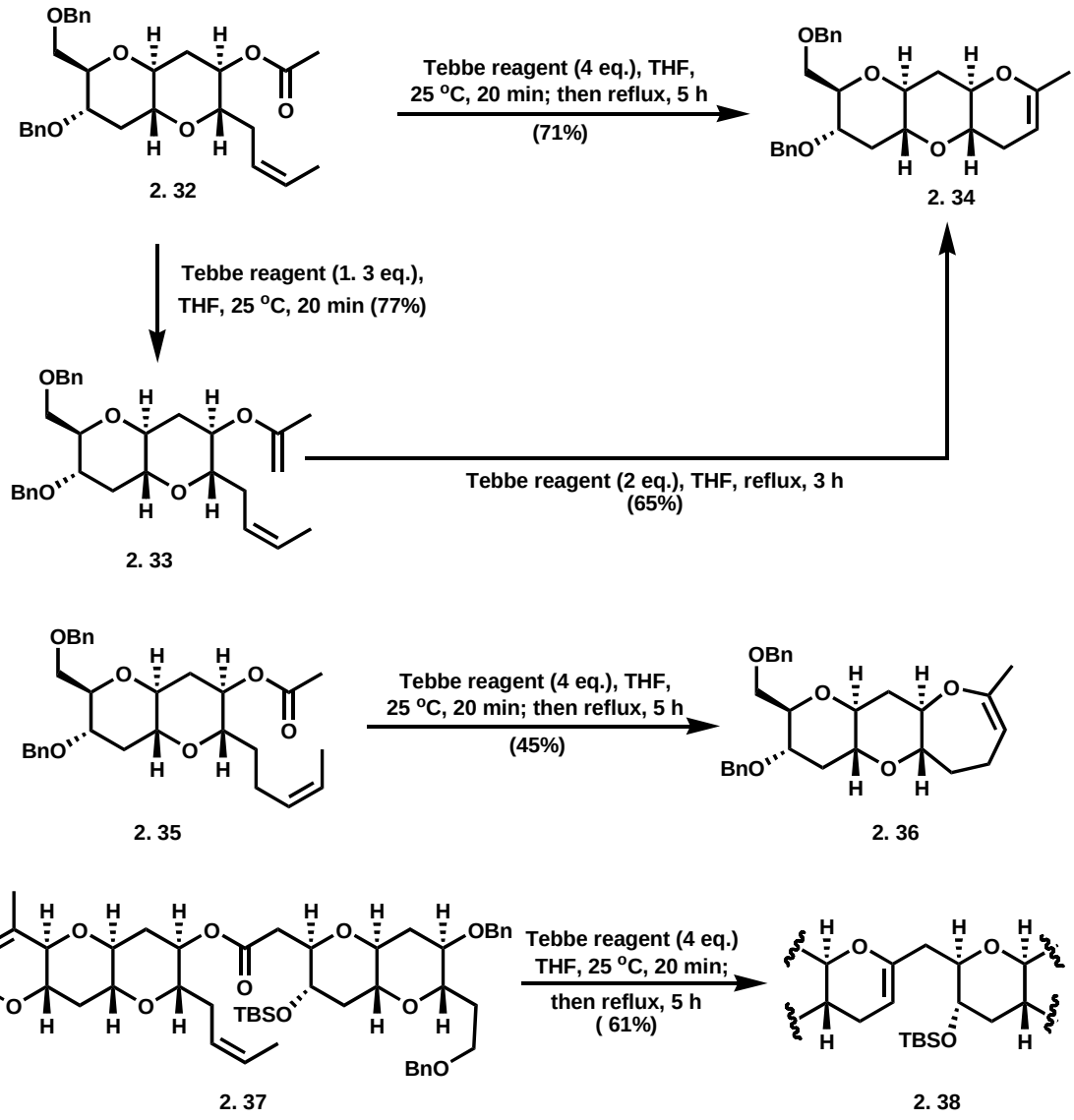
Scheme 2.9. Synthesis of capnellene using titanium reagents

Later, Nicolaou and coworkers reported a one-pot methylenation-RCM procedure using the Tebbe and the Petasis reagents.[16] Tebbe methylenation of ester **2.32** was carried out at rt to give acyclic enol ether **2.33**. Heating **2.33** with the same reagent afforded cyclic enol ether **2.34**. A combination of the two steps in a single pot proved convenient and efficient (Scheme 2.10). This process could effect the formation of seven-membered enol ether ring **2.36** in moderate yield. Complex substrate **2.37** also cyclized under these conditions to give **2.38** in 61% yield.[16]

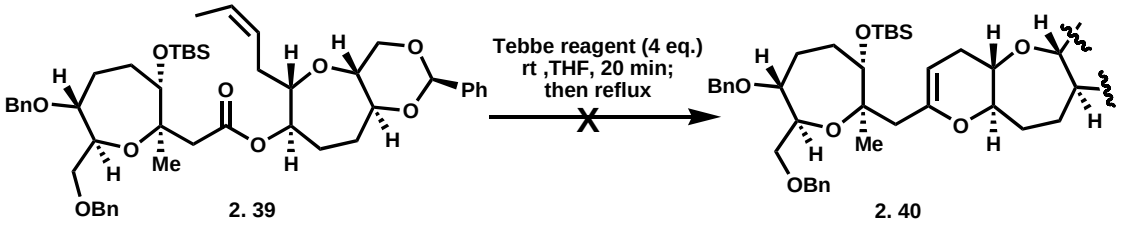
There are limitations to the use of the Tebbe reagent. Yamamoto and co-workers found Nicolaou's process to be ineffective in their approach to the gambierol G-ring.[17] All attempts to effect cyclization of **2.39** resulted in failure and none of **2.40** was obtained (Scheme 2.11).

Another impressive approach was reported by Takeda and co-workers in 2001. They reported the intramolecular carbonyl olefination using a thioacetal-$Cp_2Ti[P(OEt)_3]_2$ system.[18] The reaction was able to deliver a series of five-, six- and seven-membered cyclic enol ethers in good yield (Scheme 2.12). Five-membered cyclic enol ether **2.42** was formed in 71% yield from **2.41**. Six-membered cyclic enol ether **2.44** was formed in 56% yield from **2.43**. Seven-membered enol ether **2.46** was formed in 68% yield.

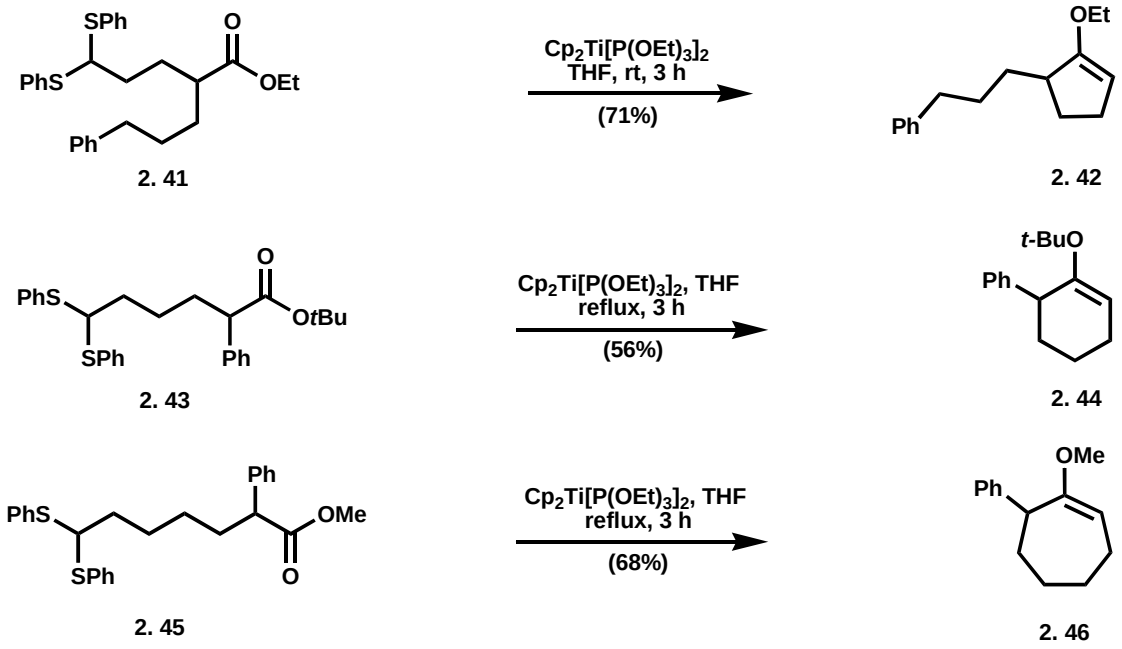
Hirama and co-workers found that the tandem methylenation-RCM was difficult when the ester was sterically hindered. During the synthesis of HIJKLM ring segment of ciguatoxin CTX3C, they found that the transformation of **2.47** to **2.48** was not reproducible using the Tebbe reagent.[19] However, the intramolecular Takeda alkylidenation of thioacetal **2.49** gave the same enol ether **2.48** reproducibly in 52-67% yield even on a one to two gram scale (Scheme 2.13).



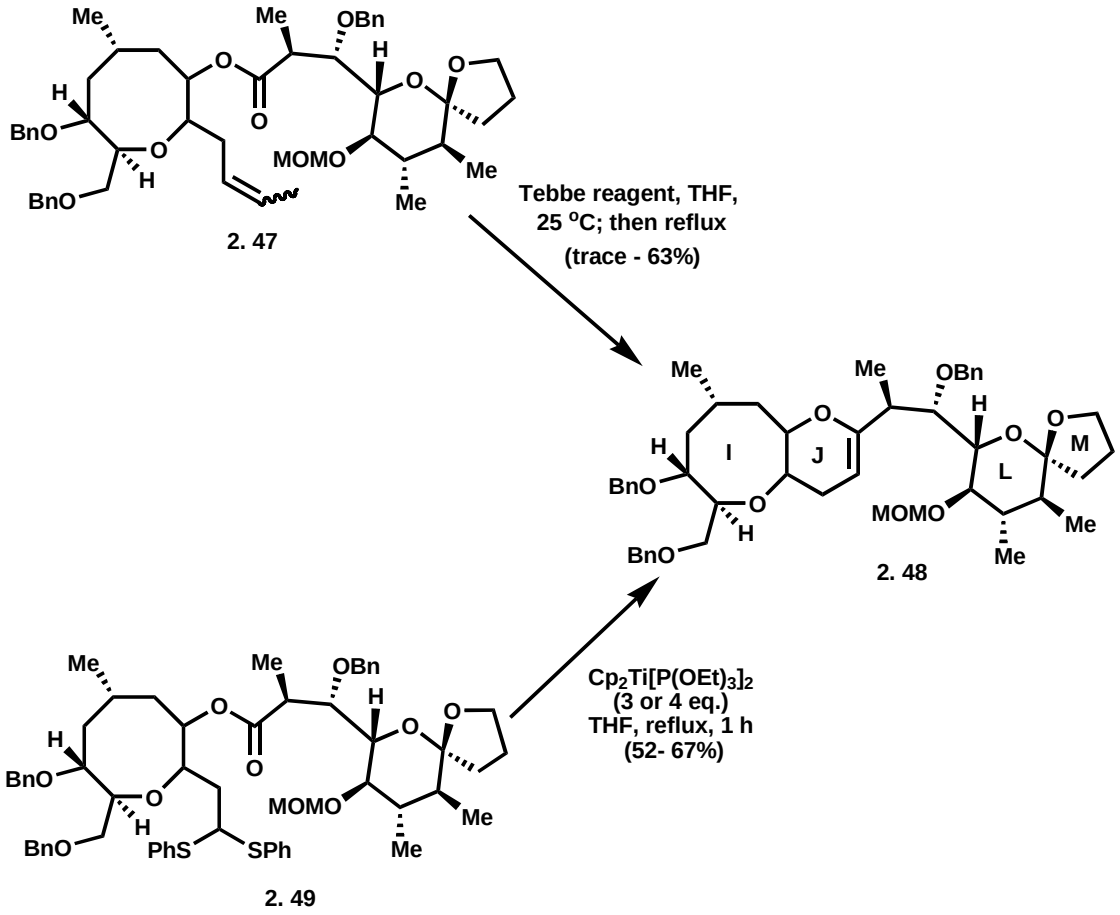
Scheme 2.10.Nicolaou's approach to effect olefinic-ester cyclizations in one pot



Scheme 2.11. Yamamoto's efforts toward to olefinic-ester cyclization



Scheme 2.12. Takeda's carbonyl olefination using $Cp_2Ti[P(OEt)_3]_2$



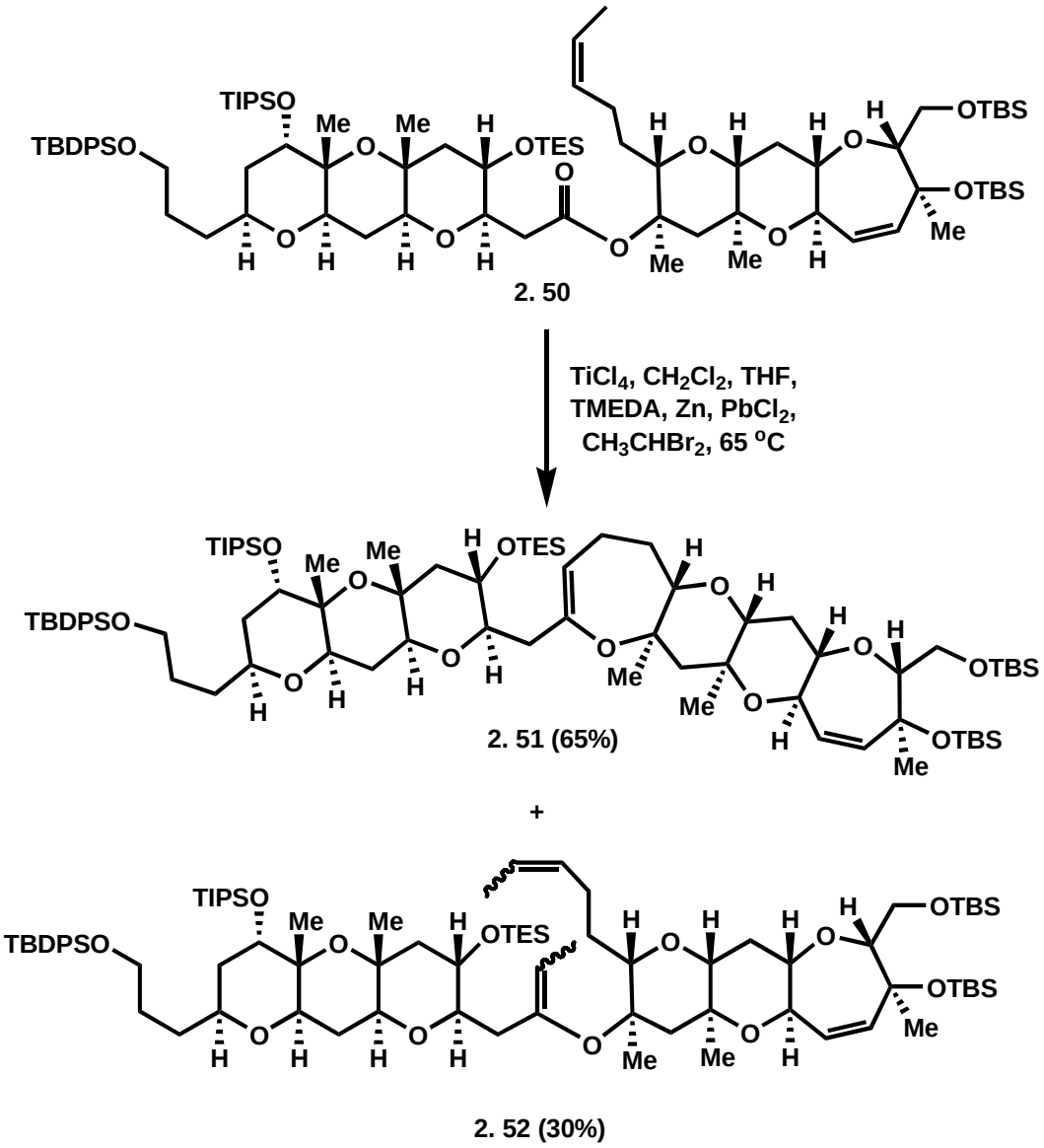
Scheme 2.13. Hirama's efforts towards the J ring in ciguatoxin CTX3C

Discovery of a titanium ethylidenereagent

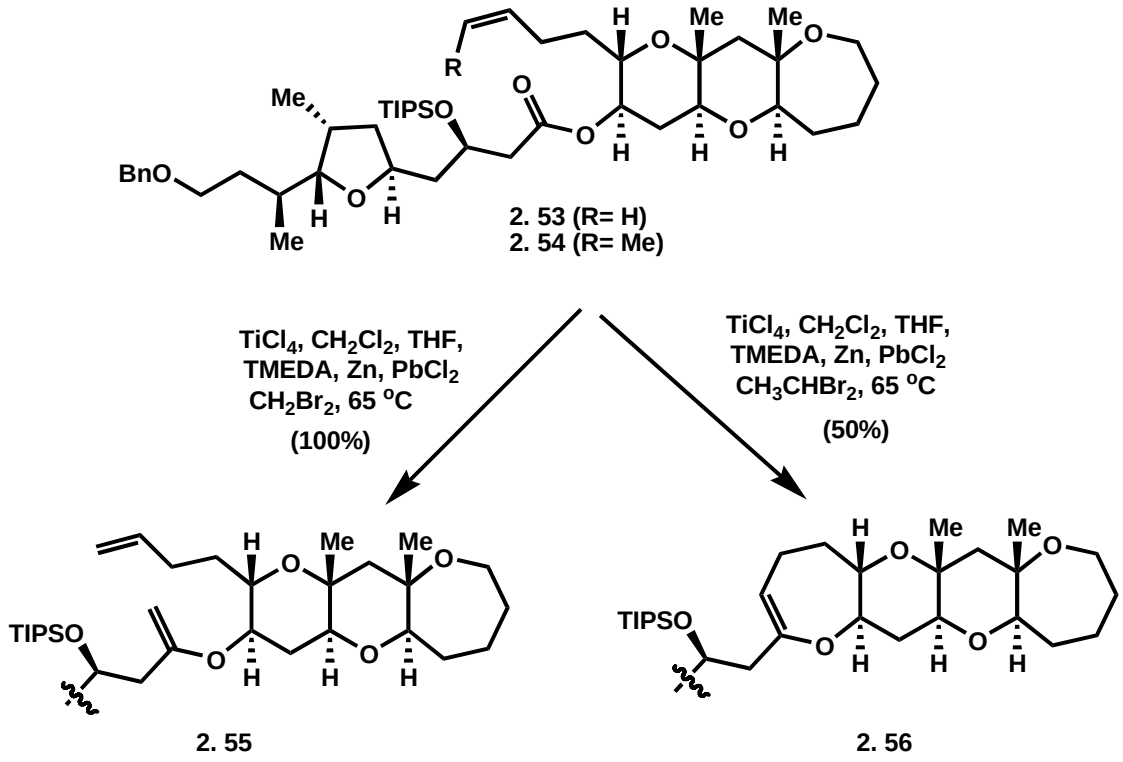
Over the past several years, our group has reported the cyclizations of olefinic-esters and olefinic-lactones using an in situ generated titanium ethylidene reagent.[20] These reactions represent a significant milestone because when compared to a two-step metathesis sequence, the methodology is more efficient. A reduced titanium reagent was chosen here because of its increased reactivity relative to dimethyltitanocene and its diminished Lewis acidity relative to the Tebbe reagent.[21] In addition, the in situ preparation of the reduced titanium and its tolerance of a wide variety of functionality makes it among the more useful titanium reagents.[22]

The special reactivity of the reduced titanium ethylidene reagent can be traced back to the mid-2000s. During the total synthesis of gambierol,[23] Henry Johnson from our group found that a related titanium methylidene reagent that comes from the use of dibromomethane as the alkylidene source decomposed the cyclization precursor. However, the use of a titanium ethylidene (utilizing dibromoethane instead of dibromomethane) gave a 2:1 mixture favoring cyclic enol ether **2.51** over acyclic enol ether **2.52** as shown in Scheme 2.14. These results showed, for the first time, the different reactivity profile between the titanium methylidene and the titanium ethylidene.

Later, in the synthesis of a model of gambieric acid A,[24] Scott Roberts also found that the cyclic to acyclic product distribution was dependent on the titanium alkylidene reagent used as shown in Scheme 2.15. If dibromomethane was used, olefinic ester **2.53** was converted to acyclic enol ether **2.55**. However, if dibromoethane was used, only cyclic enol ether **2.56** was isolated.



Scheme 2.14. End game synthesis of gambierol



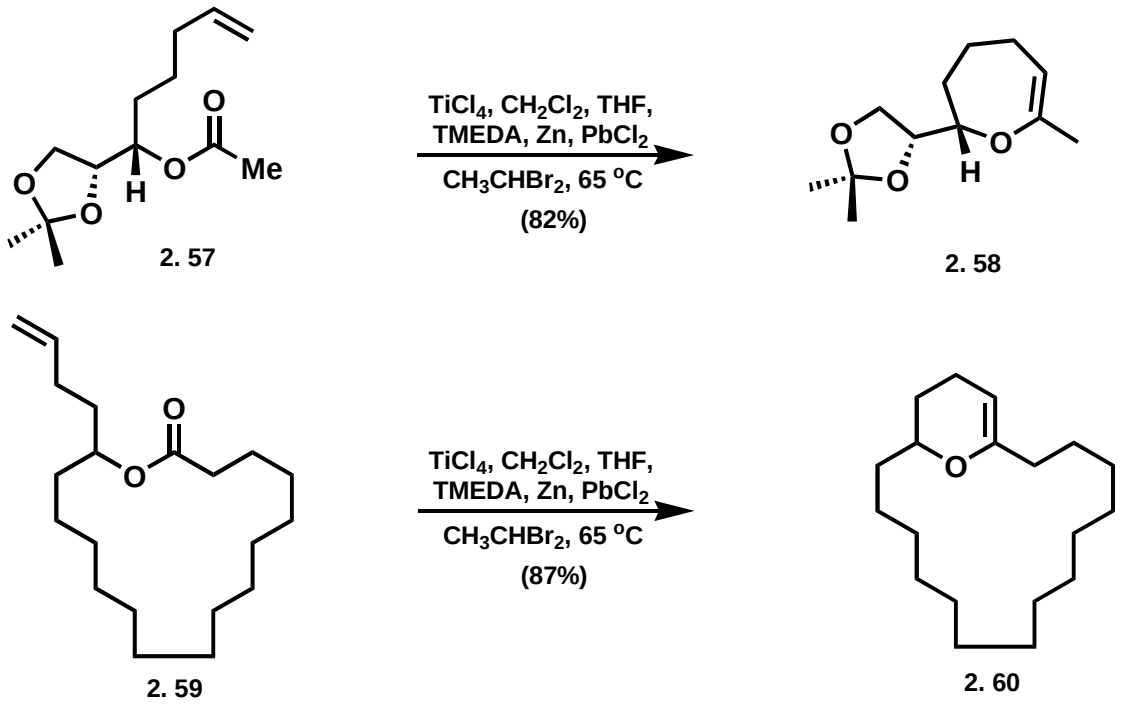
Scheme 2.15. Synthesis of A-E ring of a model of gambieric acid A

In terms of scope, we found that the titanium ethylidene can be used in olefinic-ester and olefinic-lactone cyclizations (Scheme 2.16). Linear olefinic ester **2.57** was converted to seven-membered enol ether ring **2.58** with 82% yield.[20(a)] Similarly, lactone **2.59** was converted to **2.60** in one step in 87% yield.[20(b)]

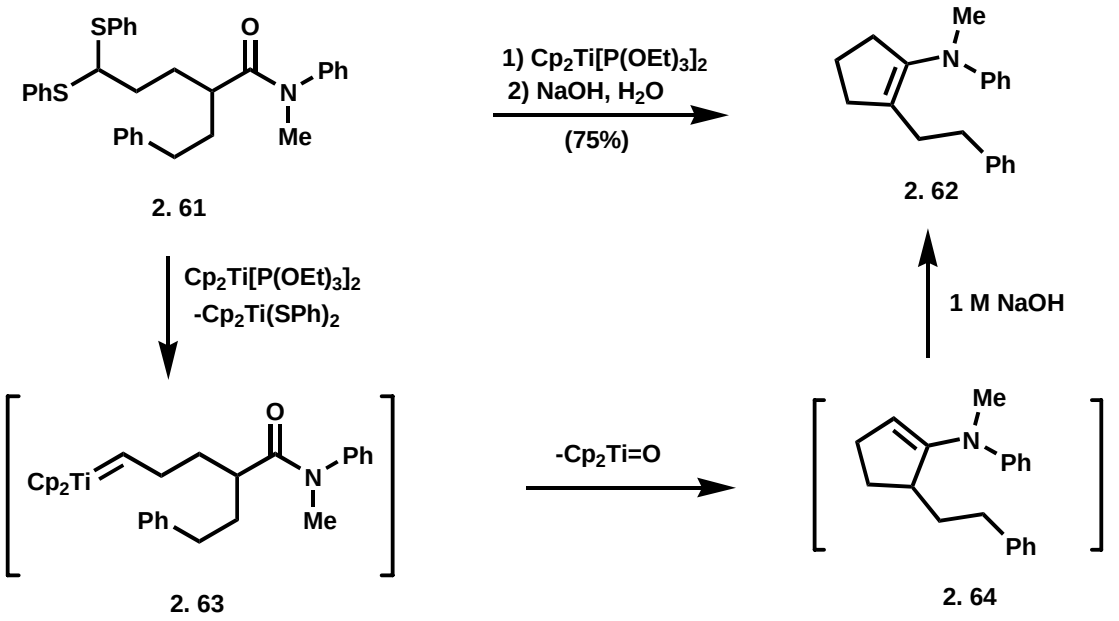
Related work on olefinic-amide cyclization

Although a substantial amount of work has been published on olefinic-ester cyclizations, there are few reports on the corresponding olefinic-amide reactions.

Takeda and co-workers reported a Ti(II)-promoted cyclization of dithianes with pendant amides as shown in Scheme 2.17. They believe the highly substituted enamine **2.62** is produced by the isomerization of the enamine **2.64**. Enamine **2.64** was formed



Scheme 2.16. Olefinic-ester and olefinic-lactone cyclizations

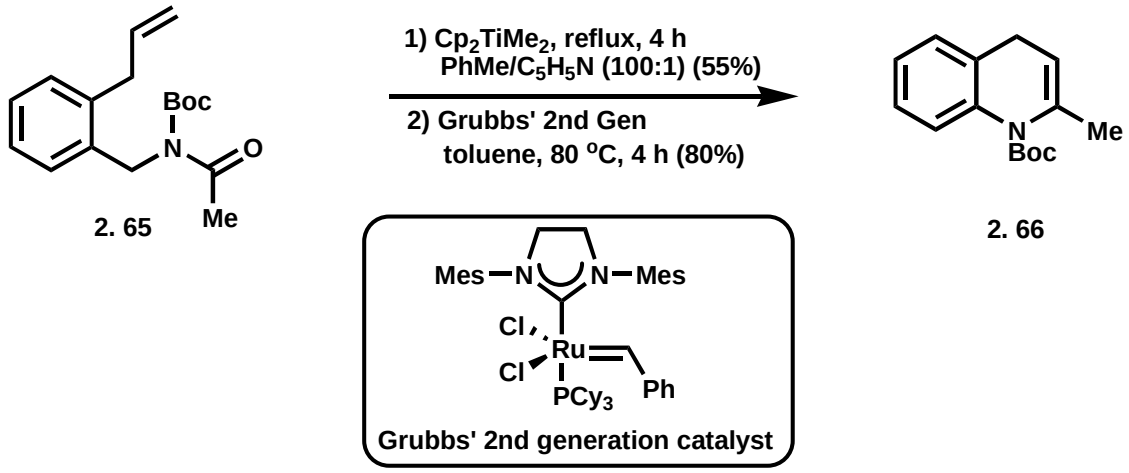


Scheme 2.17. Ti(II)-promoted reductive alkylation of anilides with thioacetals

from an intramolecular carbonyl olefination of the intermediary titanium carbene complex **2.63**.[25]

In work more closely related to that described here, Bennasar reported a methylenation/ring-closing metathesis sequence to synthesize enamide-containing benzo-fused heterocycles[26] (Scheme 2.18). They first converted amide **2.65** to the acyclic enamide using dimethyltitanocene. In the next step, Grubbs' second generation catalyst was used to convert the acyclic enamide to the corresponding cyclic enamide **2.66** in 44% overall yield for the two steps. They used this chemistry to synthesize indoles, dihydroquinolines and dihydroisoquinolines in yields that ranged from 40% to 55%.

Considering our group's work on olefinic-lactone and olefinic-ester cyclizations, we decided to expand the scope of the chemistry to olefinic-lactam and olefinic-amide cyclizations.

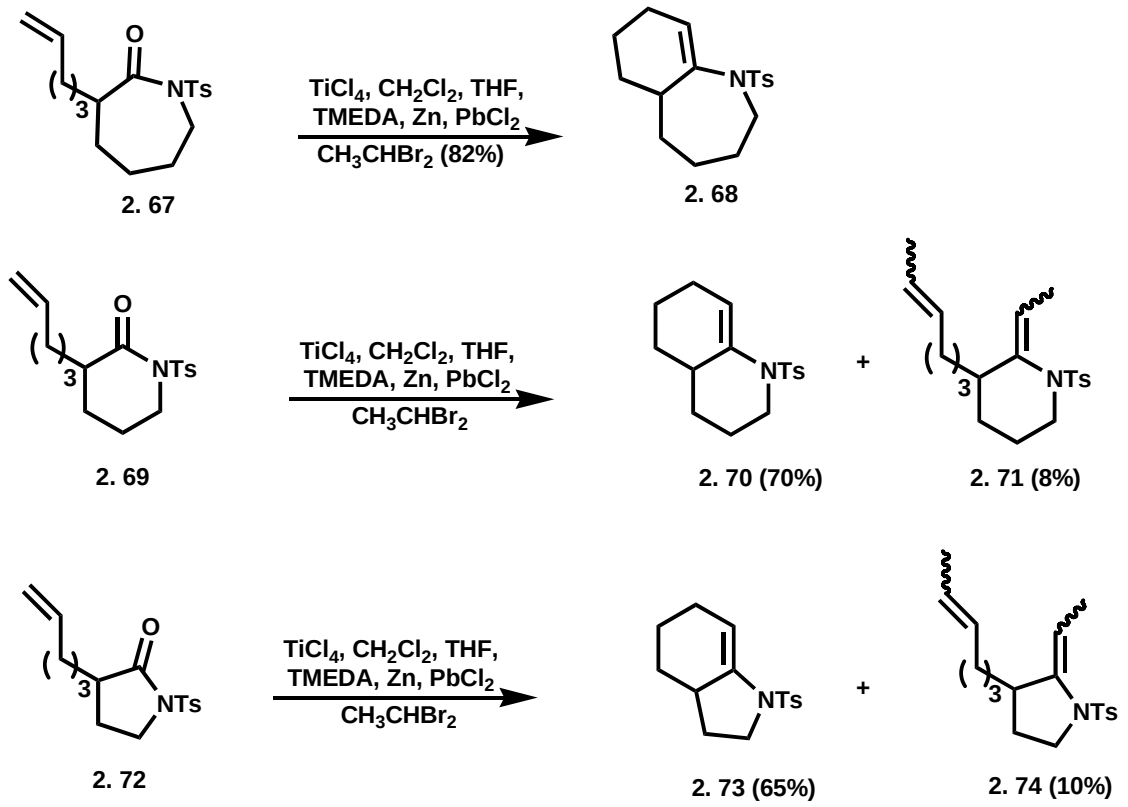


Scheme 2.18. Sequential methylenation-enamide ring-closing metathesis

Results and Discussion

We first studied the olefinic-lactam cyclizations as show in Scheme 2.19. Due to the potential reaction of the carbonyl protecting groups with the titanium reagent, we used Ts protected amides in these studies. When ε-caprolactam derivative **2.67** was subjected to the titanium ethylidene reagent, 6-membered enamide ring **2.68** was formed in 82% yield. The cyclization of δ-valerolactam derivative **2.69** and 2-pyrrolidinone derivative **2.72** also gave cyclic enamides **2.70** and **2.73** in 70% and 65% yields, respectively.[27]

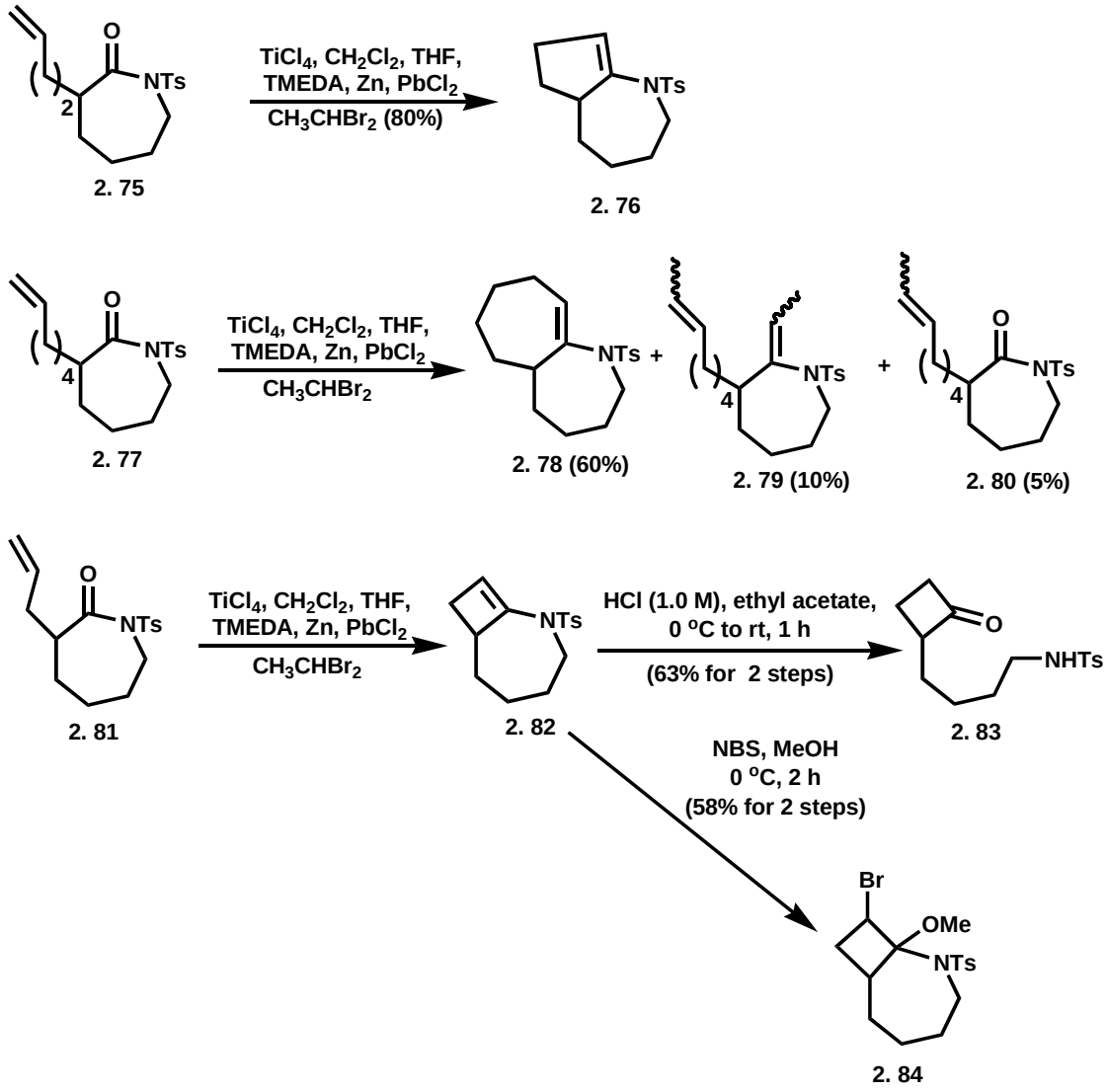
Further studies demonstrated that not only six-membered enamide ring could be formed in this way, but that five-membered and seven-membered rings could also be formed (Scheme 2.20). Cyclization of **2.75** generated five-membered enamide ring **2.76** as the exclusive product in 80% yield. Cyclization of **2.77** afforded the seven-membered ring substrate **2.78** in 60% yield, along with 10% of acyclic enamide **2.79** and 5% of lactam **2.80**.



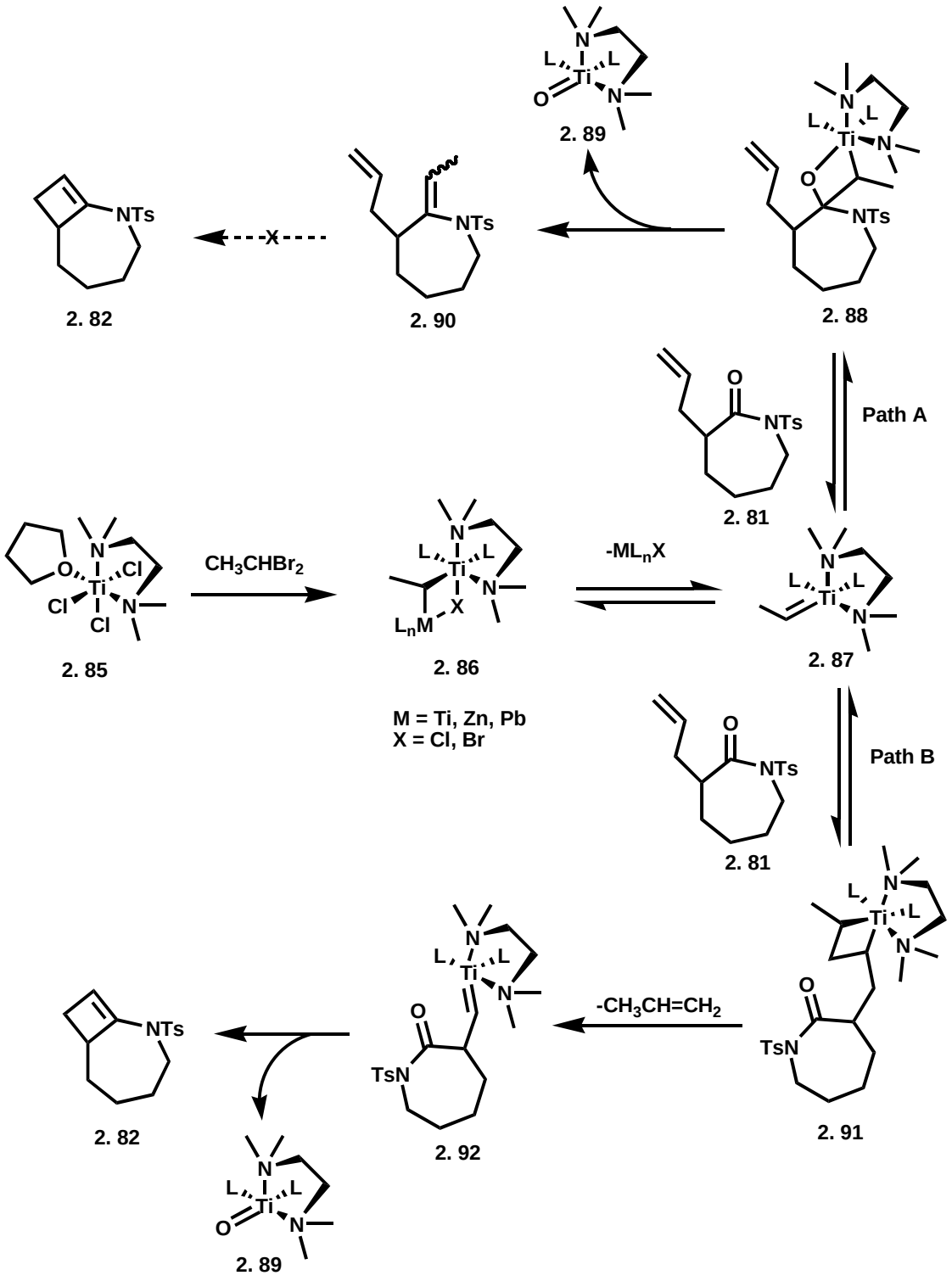
Scheme 2.19. Olefinic-lactam cyclizations

Interestingly, when ε-caprolactam derivative **2.81** was subjected to the reaction conditions, four-membered ring **2.82** was formed. Due to its instability, **2.82** was hydrolyzed to cyclobutanone **2.83** for characterization. What is more, **2.82** could be converted into useful intermediates in organic synthesis such as bromoaminal **2.84** which came from the treatment of **2.82** with NBS in methanol.

The formation of the four-membered ring substrate **2.82** provided support for our mechanistic hypothesis where olefin metathesis to give **2.92** is followed by carbonyl olefination (Scheme 2.21). It is unlikely to form the cyclobutene through metathesis of species like **2.90**.[28]

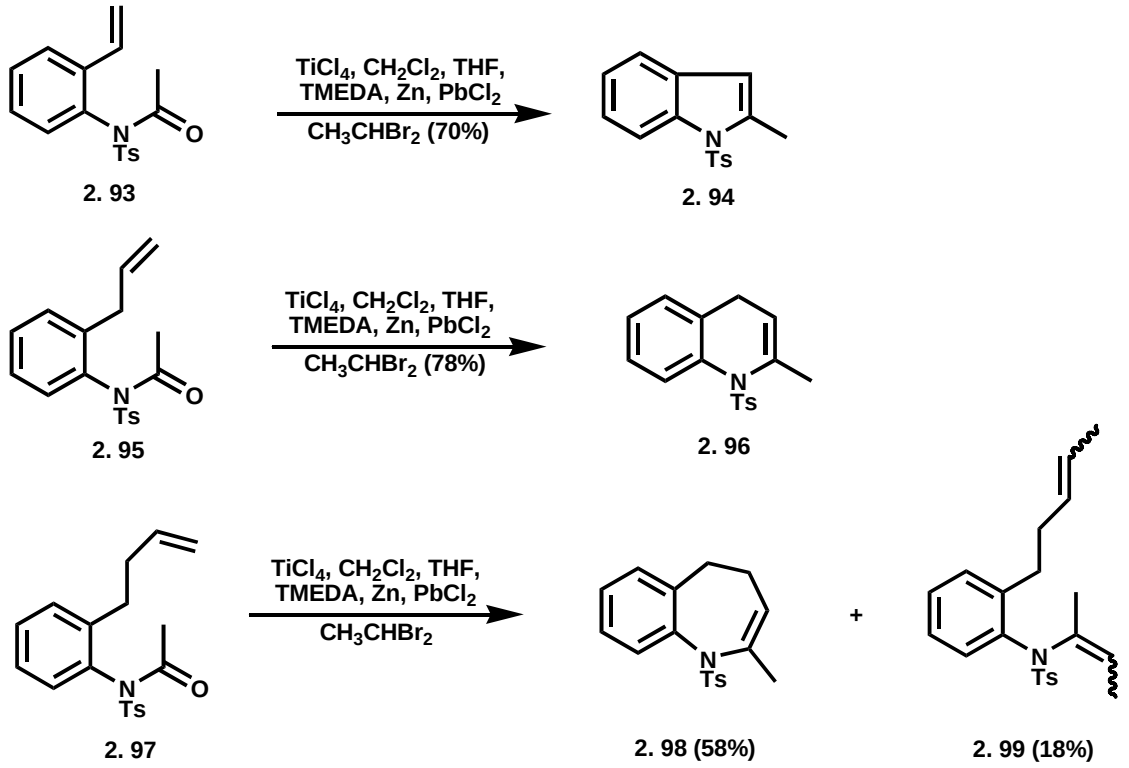


Scheme 2.20. Olefinic-lactam cyclizations

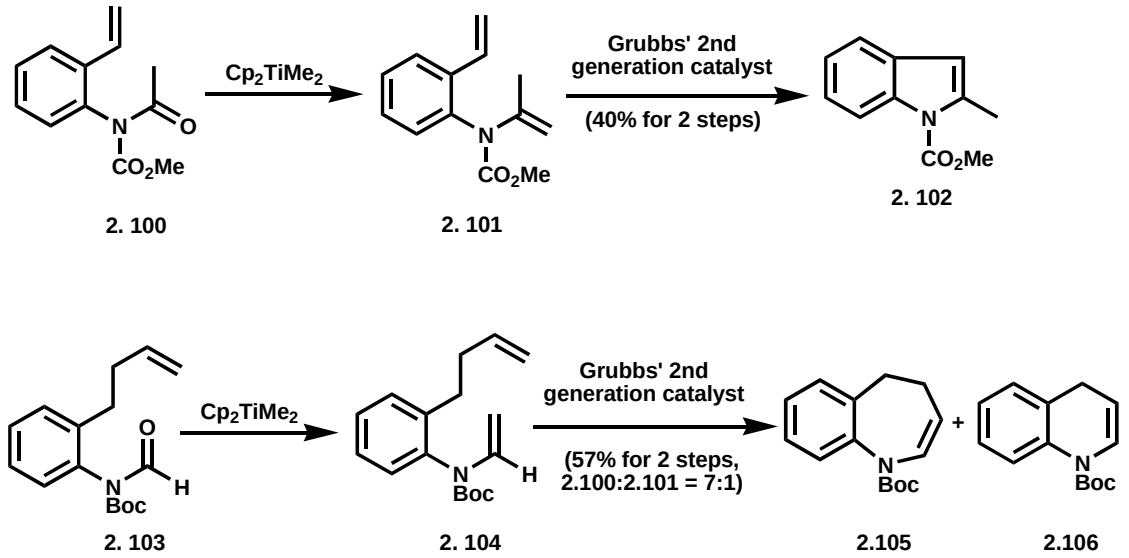


Scheme 2.21. Proposed mechanism for the generation of cyclic lactam **2.82**

Having demonstrated olefinic-lactam cyclizations, we next explored the cyclization of aromatic substrates as shown in Scheme 2.22. The cyclization of **2.93** afforded indole **2.94** with 70% yield. Bennasar's two-step protocol on a related substrate **2.100** resulted in a 40% overall yield[26] (Scheme 2.23). The cyclization of **2.95** resulted in a 78% yield of dihydroquinoline **2.96**. The more challenging cyclization of olefinic-amide **2.97** resulted in a 58% of seven-membered ring **2.98** and a 18% yield of the corresponding acyclic enamide **2.99**. When Bennasar used their two-step protocol to construct the seven-membered ring from **2.103**, they were able to isolate 50% of **2.105** and 7% of **1.106** which came from olefin isomerization and cyclization[26] (Scheme 2.23). Olefin isomerization is not a problem with the titanium alkylidene cyclization.



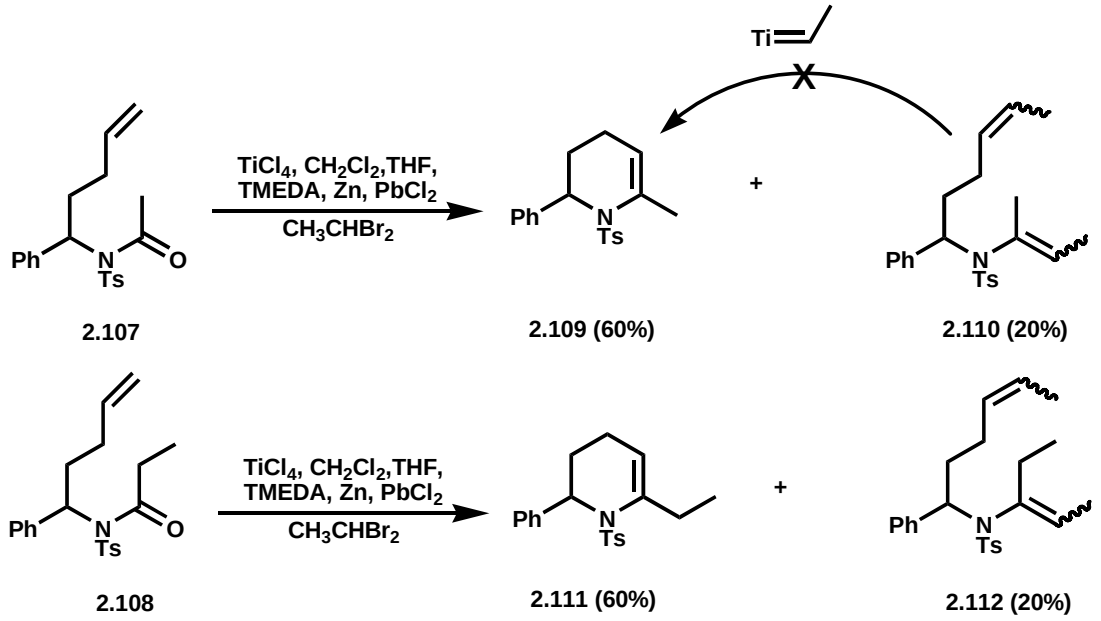
Scheme 2.22.Olefinic-amide cyclizations to benzyl fused enamides



Scheme 2.23. Bennasar'smethylenation/ring-closing metathesis

Finally, we examined the cyclization of linear amides such as **2.107** and **2.108** which lack cyclic templates (Scheme 2.24). The cyclization of **2.107** resulted in a 60% yield of cyclic enamide **2.109** and a 20% yield of acyclic enamide **2.110**. In support of the olefin metathesis, carbonyl olefination proposed in Scheme 2.21, we resubjected acyclic enamide **2.110** to the reaction conditions and did not observe the formation of cyclic enamide **2.109**. The cyclization of **2.108** also gave a similar result with a 60% of cyclic enamide **2.111** and 20% of acyclic enamide **2.112**.

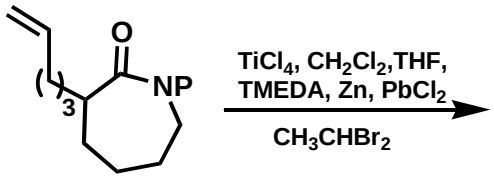
All the lactams and amides discussed above were protected with a tosyl group. The deprotection of tosyl group generally takes place under harsh conditions. In order to make this chemistry more user friendly, we tested some other protecting groups (Table 2.1). When benzyl protected substrate **2.113** was subjected to the reaction conditions, no cyclic product was observed. The reaction gave an inseparable and unidentified mixture. The nosyl group is a good replacement for tosyl group because it can be easily removed.



Scheme 2.24. Olefinic-amide cyclizations

But in the reaction of substrate **2.114**, the nosyl group was reduced, which made the reaction very messy. Boc protected olefinic-amide **2.115** gave 30% of the cyclic product, along with a number other products that made the purification very difficult.

Table 2.1. Effects of protecting groups on olefinic-lactam cyclization



Entry	Substrate	Protecting Group	Result
1	**2.113**	Bn	Inseparable mixture
2	**2.114**	Ns	Ns was reduced
3	**2.115**	Boc	30% of cyclic product

In summary, the distinct activity of titanium ethylidene reagent makes it useful not only in olefinic-ester cyclizations, but also in olefinic-amide cyclizations. This chapter has described the olefinic-amide and olefinic-lactam cyclizations using an in situ generated reduced titanium ethylidene reagent in good to excellent yields. The advantages of this reagent are obvious. It's relatively inexpensive, generated in situ and tolerant of a variety of function groups. However, the excess amount of reagents used in the reaction limits its use in large scale reactions. We will further optimize the reaction conditions and explore the scope of olefinic-carbonyl cyclization.

Experimental Section

NMR spectra were recorded on either a Varian Inova-500 MHz or a Varian VXR-500 MHz spectrometer. Chemical shifts were reported in δ, parts per million (ppm), relative to benzene (7.15) or chloroform (7.25) as internal standards. Coupling constants, *J*, were reported in Hertz (Hz) and refer to apparent peak multiplicities and not true coupling constants. Mass spectra were recorded at the Mass Spectrometry Facility at the Department of Chemistry of the University of Utah at Salt Lake City on a Finnigan MAT 95 mass spectrometer. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Solvents were purified according to the guidelines in Purification of Common Laboratory Chemicals (Perrin, Armarego, and Perrin: Oxford, 1966). $(i\text{-Pr})_2$NEt, 2,6-lutidine, TMEDA and pyridine were distilled from CaH_2. Spectroscopic grade DMF was stored over activated 4Å molecular sieves and used without purification. Zn dust (<10 μm, Aldrich) was activated by sequentially washing with HCl, H_2O, ether, and acetone and then drying under vacuum overnight. All other reagents were used without

purification. Unless otherwise stated, all reactions were run under an atmosphere of dried nitrogen in flame-dried glassware. Concentration refers to removal of solvent under reduced pressure (house vacuum at ca. 20 mmHg).

General procedure for the formation of N-tosyl protected amides:

To a cold (0 °C) solution of NaH (60% dispersion in mineral oil, 1.3 equiv.) in dry THF (4.0 mL/mmol substrate) was added a solution of amide (1.0 equiv.) in THF (1.0 mL/mmol substrate). The reaction mixture was stirred at 0 °C for 1 h. To this mixture was added a solution of tosyl chloride (1.3 equiv.) in dry THF (2.0 mL/mmol substrate) via cannula. The reaction mixture was warmed to rt over 1 h and quenched with sat. NH_4Cl (aq., 10 mL/mmol substrate) once the starting material had been completely consumed. The aqueous phase was extracted with CH_2Cl_2, dried ($MgSO_4$) and concentrated. The resulting residue was purified by flash chromatography.

General procedure for the formation of N-tosyl protected lactams:

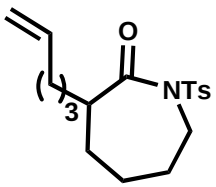
To a solution of lactam (1.0 equiv.) in THF (2 mL/mmol substrate) at 0 °C was added a solution of *n*-BuLi (1.1 equiv.) in THF (2 ml/mmol substrate). After the resulting reaction mixture had stirred for 1 h, a solution of tosyl chloride (1.3 equiv.) in THF (2.0 mL/mmol substrate) was added via cannula. The ice bath was removed after 0.5 h, the reaction mixture was warmed to rt, and the reaction was quenched with water. The aqueous phase was extracted with CH_2Cl_2, the extracts were dried ($MgSO_4$) and concentrated. The resulting residue was purified by flash chromatography.

General procedure for olefinic-amide/lactam cyclizations:

A flame-dried three-necked flask fitted with a condenser was cooled to 0 °C and charged with CH_2Cl_2 (288 mL/mmol substrate) followed by $TiCl_4$ (32 equiv.). To the

resulting solution was added THF (192 equiv.) dropwise at which time the solution turned yellow. The addition of THF was followed by the dropwise addition of TMEDA (192 equiv.) resulting in the formation of a brown solution. The ice bath was removed and the mixture was allowed to stir for 20 min. Activated Zn dust (72 equiv.) and $PbCl_2$ (3.8 equiv.) were then added. The resulting mixture went through a series of color changes from brown to green to purple and finally to blue-green over the course of 3-5 min. To the slurry was transferred a solution of lactam (1.0 equiv.) or amide (1.0 equiv.) and CH_3CHBr_2 (32 equiv.) in CH_2Cl_2 (20 mL/mmol substrate) via cannula. The reaction mixture was then heated at reflux for 2-4 h. Following this time period the mixture was cooled to 0 °C and quenched with sat. K_2CO_3 (aq., 6.5 mL/mmol substrate). After stirring for 30 min at 0 °C, the resulting mixture was filtered. The residue was washed with 1:1 hexanes:ethyl acetate (3 x 200 mL/mmol). The filtrate was combined and concentrated. The resulting residue was purified by flash chromatography.

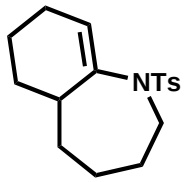
Characterization



2. 67

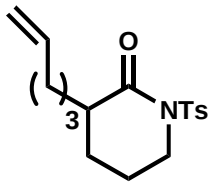
3-(pent-4-enyl)-1-tosylazepan-2-one (2.67). Prepared according to the general procedure described above using hexahydro-3-(4-penten-1-yl)-2H-azepin-2-one[29] (91 mg, 0.50 mmol), *n*-BuLi (0.34 mL of a 1.6 M solution in THF, 0.55 mmol), and tosyl chloride (124 mg, 0.650 mmol) to give 144 mg (86%) of N-tosyl protected lactam **2.67** as a colorless oil after flash chromatography (hexanes:ethyl acetate, 20:1 to 5:1). R_f 0.52

(CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 8.08 (d, *J* = 8.3 Hz, 2 H), 6.76 (d, *J* = 8.3 Hz, 2 H), 5.68 (dddd, *J* = 17.1, 10.3, 6.8, 6.8 Hz, 1 H), 4.98-4.92 (m, 2 H), 4.50 (ddd, *J* = 16.2, 3.9, 3.9 Hz, 1 H), 2.95-2.90 (m, 1 H), 1.97-1.84 (m, 3 H), 1.82 (s, 3 H), 1.73-1.66 (m, 1 H), 1.38-0.92 (m, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 175.3, 143.8, 138.8, 138.3, 129.2, 129.1, 114.7, 45.7, 45.1, 34.2, 32.0, 30.0, 28.7, 28.1, 26.8, 21.1; IR (neat) 3062, 2934, 2860, 1700, 1350, 1168, 1107, 1089 cm^{-1}; LRMS (ESI) calcd for $C_{18}H_{25}NO_3SNa$ 358.1 ($M+Na^+$), found 358.1.



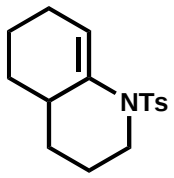
2. 68

1-tosyl-2,3,4,5,5a,6,7,8-octahydro-1H-benzo[b]azepine (2.68). The general cyclization protocol was carried out on lactam **2.67** (25 mg, 0.075 mmol) using $TiCl_4$(0.26 mL, 2.4 mmol) in CH_2Cl_2 (21.5 mL), THF (1.26 mL, 14.4 mmol), TMEDA (2.15 mL, 14.4 mmol), activated Zn dust (350 mg, 5.4 mmol), $PbCl_2$ (79 mg, 0.28 mmol), and CH_3CHBr_2 (0.22 mL, 2.4 mmol) in CH_2Cl_2 (1.4 mL + 1.4 mL rinse) to give 19 mg (82 %) of **2.68** as a colorless oil after flash chromatography (hexanes:ethyl acetate, 20:1 to 10:1 to 5:1). R_f 0.52 (CH_2Cl_2);^{1}H NMR (500 MHz, C_6D_6) δ 7.80 (d, *J* = 7.8 Hz, 2 H), 6.80 (d, *J* = 7.8 Hz, 2 H), 5.56-5.55 (m, 1 H), 3.59 (ddd, *J* = 12.7, 7.8, 4.4 Hz 1 H), 3.14 (ddd, *J* = 12.2, 7.3, 3.4 Hz, 1 H), 2.24-2.20 (m, 1 H), 1.89 (s, 3 H), 1.88-1.82 (m, 1 H), 1.77-1.70 (m, 1 H), 1.64-1.56 (m, 1 H), 1.52-1.46 (m, 1 H), 1.41-1.09 (m, 7 H); ^{13}C NMR (125 MHz, C_6D_6) δ 142.3, 140.9, 139.4, 129.3, 127.6, 127.6, 50.6, 38.8, 33.8, 30.3, 28.8, 25.44, 25.41, 21.1, 19.6; IR (neat) 2929, 2858, 1450, 1340, 1158, 1112, 1090 cm^{-1}; LRMS (ESI) calcd for $C_{17}H_{24}NO_2S$ 306.2 (MH^+), found 306.1.



2. 69

3-(pent-4-enyl)-1-tosylpiperidin-2-one (2.69). Prepared according to the general tosylate forming procedure using3-(4-penten-1-yl)- 2-piperidinone[30] (91 mg, 0.50 mmol), *n*-BuLi (0.34 mL of a 1.6 M solution in THF, 0.55 mmol), and tosyl chloride (124 mg, 0.650 mmol) to give 141 mg (88%) of N-tosyl protected lactam **2.69** as a colorless oil following flash chromatography (hexanes:ethyl acetate, 20:1 to 5:1). R_f 0.77 (CH_2Cl_2:CH_3OH, 10:1); ^{1}H NMR (500 MHz, C_6D_6) δ 8.08 (d, *J* = 8.3 Hz, 2 H), 6.80 (d, *J* = 8.3 Hz, 2 H), 5.64 (dddd, *J* = 16.6, 10.3, 6.4, 6.4 Hz, 1 H), 4.95-4.91 (m, 2 H), 3.66-3.56 (m, 2H), 1.84 (s, 3 H), 1.81-1.71 (m, 3 H), 1.66-1.60 (m, 1H), 1.29-1.22 (m, 1H), 1.19-1.02 (m, 5H), 0.79-0.71 (m, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 172.5, 144.0, 138.6, 137.6, 129.2, 114.7, 46.5, 43.3, 33.9, 30.6, 26.3, 25.6, 22.2, 21.1; IR (neat) 3072, 2932, 2867, 1694, 1352, 1168, 1120, 1090 cm^{-1}; LRMS (ESI) calcd for $C_{17}H_{23}NO_3SNa$ 344.1 ($M+Na^+$), found 344.1.

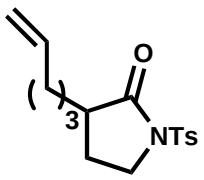


2. 70

1-tosyl-1,2,3,4,4a,5,6,7-octahydroquinoline (2.70). The general cyclization protocol was carried out on lactam **2.69** (26 mg, 0.081 mmol) using $TiCl_4$ (0.28 mL, 2.6 mmol) in CH_2Cl_2 (23 mL), THF (1.37 mL, 15.6 mmol), TMEDA (2.32 mL, 15.6 mmol), activated Zn dust (378 mg, 5.82 mmol), $PbCl_2$ (86. mg, 0.31 mmol), and CH_3CHBr_2 (0.24

mL, 2.6 mmol) in CH_2Cl_2 (1.5 mL + 1.5 mL rinse) to give 16.5 mg (70 %) of **2.70** and 2.2 mg (8%) of the corresponding acyclic enamide **2.71** as colorless oils after flash chromatography (hexanes:ethyl acetate, 20:1 to 10:1 to 5:1). Data for **2.70**: R_f 0.53 (hexanes:ethyl acetate, 3:1); ^{1}H NMR (500 MHz, C_6D_6) δ 7.80 (d, *J* = 8.3 Hz, 2 H), 6.76 (d, *J* = 8.3 Hz, 2 H), 6.11 (dd, *J* = 5.3, 2.9 Hz, 1 H), 4.36-4.31 (m, 1 H), 2.79-2.73 (m, 1 H), 1.99-1.92 (m, 1 H), 1.86 (s, 3 H), 1.85-1.79 (m, 1 H), 1.58-1.51 (m, 1 H), 1.40-1.35 (m, 2 H), 1.28-1.18 (m, 3 H), 1.04-1.00 (m, 1 H), 0.92-0.71 (m, 2 H); ^{13}C NMR (125 MHz, C_6D_6) δ 142.4, 140.1, 137.4, 129.4, 128.3, 124.7, 48.1, 35.3, 32.7, 31.3, 25.6, 24.9, 21.6, 21.1; IR (neat) 3056, 2931, 2857, 1452, 1337, 1265, 1158, 1087 cm^{-1}; LRMS (ESI) calcd for $C_{16}H_{21}NO_2SNa$ 314.1 ($M+Na^+$), found 314.1.

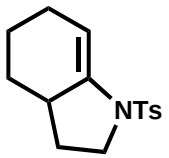
Acyclic enamide**2.71**: ^{1}H NMR (500 MHz, C_6D_6) δ 7.84-7.78 (m,3 H), 6.78-6.74 (m, 2 H), 5.75-5.71 (m, 1 H), 5.51-5.32 (m, 3 H), 4.14-4.11 (m, 1 H), 2.76-2.74 (m, 1 H), 2.40 (m, 1 H), 1.89-1.83 (m, 11 H), 1.74-1.60 (m, 8 H), 1.47-1.32 (m, 27 H); IR (neat) 2925, 2856, 1711, 1452, 1339, 1267, 1160, 1092, 706 cm^{-1}; LRMS (ESI) calcd for $C_{20}H_{29}NO_2SNa$ 370.2 ($M+Na^+$), found 370.2.



2. 72

3-(pent-4-enyl)-1-tosylpyrrolidin-2-one (2.72). Prepared according to the general tosylate forming procedure described above using3-(4-penten-1-yl)-2-pyrrolidinone[29] (77 mg, 0.50 mmol), *n*-BuLi (0.34 mL of a 1.6 M solution in THF, 0.55 mmol), and tosyl chloride (124 mg, 0.650 mmol) to give 130 mg (85%) of N-tosyl protected lactam **2.72** as a colorless oil following flash chromatography (hexanes:ethyl

acetate, 20:1 to 5:1). R_f 0.40 (hexanes:ethylacetate, 3:1); ^{1}H NMR (500 MHz, C_6D_6) δ 8.10 (d, *J* = 8.3 Hz, 2 H), 6.74 (d, *J* = 8.3 Hz, 2 H), 5.59 (dddd, *J* = 16.2, 11.2, 6.8, 6.8 Hz, 1 H), 4.92-4.88 (m, 2 H), 3.54 (ddd, *J* = 9.8, 8.8, 2.5 Hz, 1 H), 3.16 (ddd, *J* = 9.3, 9.3, 7.3 Hz 1H), 1.79 (s, 3 H), 1.74-1.69 (m, 2 H), 1.60-1.45 (m, 2H), 1.17-1.11 (m, 1H), 1.04-0.71 (m, 4H); ^{13}C NMR (125 MHz, C_6D_6) δ 172.4, 144.5, 138.3, 136.6, 129.5, 128.6, 114.8, 45.2, 42.7, 33.6, 29.7, 26.2, 24.6, 21.1; IR (neat) 2930, 2857, 1699, 1347, 1166, 1088 cm^{-1}; LRMS (ESI) calcd for $C_{16}H_{22}NO_3S$ 308.1 ($M+H^+$), found 308.1.

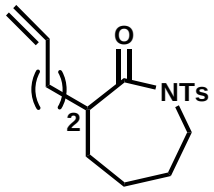


2. 73

1-tosyl-2,3,3a,4,5,6-hexahydro-1H-indole (2.73). The general cyclization protocol was carried out on lactam **2.72 (**19 mg, 0.062 mmol) using $TiCl_4$ (0.22 mL, 2.0 mmol) in CH_2Cl_2 (18 mL), THF (1.04 mL, 11.9 mmol), TMEDA (1.77 mL, 11.9 mmol), activated Zn dust (289 mg, 4.45 mmol), $PbCl_2$ (65 mg, 0.23 mmol), and CH_3CHBr_2 (0.18 mL, 2.0 mmol) in CH_2Cl_2 (1.2 mL + 1.2 mL rinse) to give 11 mg (65 %) of **2.73** and 2 mg (10%) of the corresponding acyclic enamide **2.74** as colorless oils after flash chromatography (hexanes:ethyl acetate, 20:1 to 10:1 to 5:1). Data for **2.73**: R_f 0.55 (hexanes:ethyl acetate, 3:1); ^{1}H NMR (500 MHz, C_6D_6) δ 7.80 (d, *J* = 7.8 Hz, 2 H), 6.76 (d, *J* = 7.8 Hz, 2 H), 6.07 (dd, *J* = 6.4, 3.5 Hz, 1 H), 3.61 (dd, *J* = 8.8, 8.8 Hz, 1 H), 2.96 (ddd, *J* = 10.7, 9.7, 5.8, 1 H), 2.03-1.88 (m, 2 H), 1.84 (s, 3 H), 1.49-1.40 (m, 3 H), 1.19 (ddd, *J* = 11.7, 6.3, 6.3 Hz, 1 H), 1.08-0.98 (m, 1 H), 0.85-0.69 (m, 2 H); ^{13}C NMR (125 MHz, C_6D_6) δ 143.0, 139.9, 136.1, 129.4, 127.7, 105.0, 49.2, 39.5, 29.4, 28.3, 24.1, 22.0,

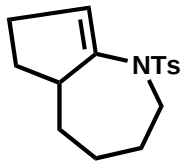
21.0; IR (neat) 3055, 2987, 2926, 2850, 1420, 1362, 1266, 1222, 1164, 1091 cm^{-1}; LRMS (ESI) calcd for $C_{15}H_{19}NO_2SNa$ 300.1 ($M+Na^+$), found 300.1.

Acyclic enamide **2.74**: ^1H NMR (500 MHz, C_6D_6) δ 7.80 (d, *J* = 8.3 Hz, 2 H), 7.76 (d, *J* = 7.82 Hz, 2 H), 6.75 (m, 4 H), 5.33-5.22 (m, 3 H), 3.52-3.46 (m, 1 H), 3.33-3.23 (m, 2 H), 2.2 (m, 2 H), 1.89-1.80 (m, 10 H), 1.73-1.68 (m, 4 H), 1.58-1.57 (m, 6 H), 1.50-1.46 (m, 4 H), 1.35-1.18 (m, 7 H), 1.14-1.06 (m, 3 H), 1.01-0.70 (m, 16 H), 0.57 (t, 1 H); IR (neat) 2930, 1349, 1165, 1092 cm^{-1}; LRMS (ESI) calcd for $C_{19}H_{27}NO_2SNa$ 356.2 ($M+Na^+$), found 356.2.



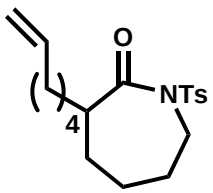
2. 75

3-(but-3-enyl)-1-tosylazepan-2-one (2.75). Prepared according to the general procedure described above using hexahydro-3-(3-buten-1-yl)-2H-azepin-2-one[30] (84 mg, 0.50 mmol), *n*-BuLi (0.34 mL of a 1.6 M solution in THF, 0.55 mmol), and tosyl chloride (124 mg, 0.650 mmol) to give 135 mg (84%) of N-tosyl protected lactam **2.75** as a colorless oilafter flash chromatography (hexanes:ethyl acetate, 20:1 to 5:1). R_f 0.39 (hexanes:ethyl acetate, 3:1); ^1H NMR (500 MHz, C_6D_6) δ 8.07 (d, *J* = 8.3 Hz, 2 H), 6.79 (d, *J* = 8.3 Hz, 2 H), 5.64-5.56 (m, 1 H), 4.92-4.88 (m, 2 H), 4.50 (ddd, *J* = 16.1, 3.9, 2.9 Hz, 1 H), 2.96 (ddd, *J* = 15.6, 9.8, 2.4 Hz, 1H), 2.07-2.02 (m,1 H), 1.89-1.78 (m, 3 H), 1.83 (s, 3 H), 1.37-1.28 (m, 3H), 1.14-1.07 (m, 2 H), 0.94 (m, 2 H); ^{13}C NMR (125 MHz, C_6D_6) δ 175.3, 143.9, 138.5, 138.1, 129.2, 127.8, 115.0, 45.1, 44.7, 31.5, 31.4, 29.8, 28.7, 28.0, 21.1; IR (neat) 3060, 2935, 2860, 1699, 1348, 1167, 1088 cm^{-1}; LRMS (ESI) calcd for $C_{17}H_{23}NO_3SNa$ 344.1 ($M+Na^+$), found 344.1.



2. 76

1-tosyl-1,2,3,4,5,5a,6,7-octahydrocyclopenta[b]azepine (2.76). The general cyclization protocol was carried out on lactam **2.75** (15 mg, 0.047 mmol) using $TiCl_4$ (0.165 mL, 1.51 mmol) in CH_2Cl_2 (13.5 mL), THF (0.79 mL, 9.0 mmol), TMEDA (1.35 mL, 9.07 mmol), activated Zn dust (219 mg, 3.37 mmol), $PbCl_2$ (50 mg, 0.18 mmol), and CH_3CHBr_2 (0.137 mL, 1.50 mmol) in CH_2Cl_2 (1.0 mL + 1.0 mL rinse) to give 10.9 mg (80 %) of **2.76** as a colorless oil following flash chromatography (hexanes:ethyl acetate, 20:1 to 10:1 to 5:1). R_f 0.56 (hexanes:ethyl acetate, 3:1); ^{1}H NMR (500 MHz, C_6D_6) δ 7.78 (d, *J* = 8.3 Hz, 2 H), 6.75 (d, *J* = 7.9 Hz, 2 H), 5.85 (dd, *J* = 4.4, 2.5 Hz, 1 H), 4.24-4.19 (m, 1 H), 2.73-2.67 (m, 1 H), 2.23-2.07 (m, 2 H), 1.85 (s, 3 H), 1.82-1.75 (m, 1 H), 1.54-1.09 (m, 6 H), 1.02-0.94 (m, 1 H), 0.87-0.76 (m, 1 H); ^{13}C NMR (125 MHz, C_6D_6) δ 144.2, 142.7, 138.4, 129.3, 127.7 115.8, 49.3, 46.5, 34.8, 32.5, 29.7, 29.6, 28.7, 21.0; IR (neat) 2922, 2850, 1450, 1343, 1160, 1090 cm^{-1}; LRMS (ESI) calcd for $C_{16}H_{21}NO_2SNa$ 314.1 ($M+Na^+$), found 314.1.

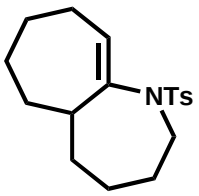


2. 77

3-(hex-5-enyl)-1-tosylazepan-2-one (2.77). To a solution of ε-caprolactam (95 mg, 0.80 mmol) in THF (5 mL) at 0 °C was added *n*-BuLi (0.65 mL of a 2.5 M solution in hexane, 1.6 mmol) dropwise. The resulting reaction mixture was stirred for 1 h, after

which 6-bromo-1-hexene (0.11 mL, 0.80 mmol) was added. The reaction was quenched after 1 h by pouring the mixture into sat. NaCl (aq., 10 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to give a pale brown oil which was taken to the next step without further purification.

The oil from above was subjected to the general tosylation procedure using *n*-BuLi (0.344 mL of a 1.6 M solution in THF, 0.55 mmol), and tosyl chloride (124 mg, 0.650 mmol) to give 142 mg (51% for 2 steps) of N-tosyl protected lactam **2.77** as a colorless oil after flash chromatography (hexanes:ethyl acetate, 20:1 to 5:1). R_f 0.43 (hexanes:ethyl acetate, 3:1); ^{1}H NMR (500 MHz, C_6D_6) δ 8.09 (d, *J* = 8.3 Hz, 2 H), 6.75 (d, *J* = 8.3 Hz, 2 H), 5.72 (dddd, *J* = 17.1, 10.3, 6.8, 6.8 Hz, 1 H), 5.01-4.95 (m, 2 H), 4.50 (ddd, *J* = 16.1, 3.4, 3.4 Hz, 1 H), 2.89 (ddd, *J* = 15.6, 6.4, 6.4 Hz, 1 H), 1.95-1.87 (m, 3 H), 1.80 (s, 3 H), 1.74-1.67 (m, 1 H), 1.37-0.88 (m, 11 H); ^{13}C NMR (125 MHz, C_6D_6) δ 175.4, 143.8, 139.0, 138.2, 129.2, 129.1, 114.5, 45.8, 45.1, 33.9, 32.3, 30.0, 29.3, 28.8, 28.1, 27.0, 21.1; IR (neat) 2929, 2857, 1700, 1348, 1166 cm^{-1}; LRMS (ESI) calcd for $C_{19}H_{27}NO_3SNa$ 372.2 ($M+Na^+$), found 372.2.

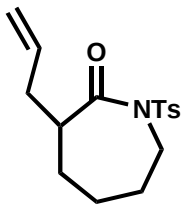


2. 78

(E)-1-tosyl-1,2,3,4,5,5a,6,7,8,9-decahydrocyclohepta[b]azepine (2.78). The general cyclization protocol was carried out on lactam **2.77** (31 mg, 0.089 mmol) using $TiCl_4$ (0.31 mL, 2.9 mmol) in CH_2Cl_2 (26 mL), THF (1.5 mL, 17 mmol), TMEDA (2.50 mL, 16.8 mmol), activated Zn dust (417 mg, 6.41 mmol), $PbCl_2$ (94 mg, 0.33 mmol), and

CH_3CHBr_2 (0.26 mL, 2.8 mmol) in CH_2Cl_2 (1.7 mL + 1.7 mL rinse) to give 17 mg (60 %) of **2.78** and 2.7 mg (10%) of the corresponding acyclic enamide **2.79** as colorless oils after flash chromatography (hexanes:ethyl acetate, 20:1 to 10:1 to 5:1). Data for **2.78**: R_f 0.56 (hexanes:ethyl acetate, 3:1); ^{1}H NMR (500 MHz, C_6D_6) δ 7.82 (d, *J* = 7.8 Hz, 2 H), 6.79 (d, *J* = 7.8 Hz, 2 H), 5.72 (dd, *J* = 6.8, 6.8 Hz, 1 H), 3.76 (ddd, *J* = 13.2, 4.4 Hz, 1 H), 2.95 (ddd, *J* = 13.2, 10.3, 3.0 Hz, 1 H), 2.33 (dd, *J* = 9.8, 9.8 Hz, 1 H), 1.89 (s, 3 H), 1.85-1.55 (m, 7 H), 1.51-1.23 (m, 6 H), 1.11-1.04 (m, 1 H); ^{13}C NMR (125 MHz, C_6D_6) δ 142.1, 140.2, 132.6, 129.3, 128.3, 128.2, 52.4, 45.1, 33.5, 32.4, 30.5, 29.3, 27.3, 26.9, 25.9, 21.1;IR (neat) 3282, 2928, 1599, 1328, 1160, 1093 cm^{-1}; LRMS (ESI) calcd for $C_{18}H_{27}NO_3SNa$ 342.1 ($M+Na^+$), found 342.1.

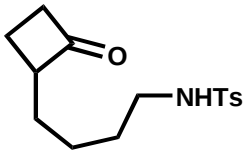
Acyclic enamide **2.79**: ^{1}H NMR (500 MHz, C_6D_6) δ 8.09 (d, *J* = 7.82 Hz, 2 H), 6.75 (d, *J* = 7.81 Hz, 2 H), 5.46-5.34 (m, 2 H), 4.51-4.47 (m, 1 H), 2.9 (m, 1 H), 1.95-1.89 (m, 2 H), 1.81 (s, 3 H), 1.74 (m, 1 H), 1.59 (m, 2 H), 1.52-1.48 (m, 1 H), 1.35-1.30 (m, 3 H), 1.26-1.22 (m, 1 H), 1.18-1.16 (m, 2 H), 1.13-1.02 (m, 3 H), 1.0-0.93 (m, 2 H), 0.83 (m, 1 H); IR (neat) 2928, 2856, 1700, 1597, 1348, 1166, 1087 cm^{-1}; LRMS (ESI) calcd for $C_{22}H_{33}NO_2SNa$ 386.2 ($M+Na^+$), found 386.2.



2. 81

3-allyl-1-tosylazepan-2-one (2.81). Prepared according to the general procedure described above using hexahydro-3-(2-propen-1-yl)-2H-azepin-2-one[31] (77 mg, 0.50 mmol), *n*-BuLi (0.34 mL of a 1.6 M solution in THF, 0.55 mmol), and tosyl chloride

(124 mg, 0.650 mmol) to give 131 mg (85%) of N-tosyl protected lactam **2.81** as a colorless oil after flash chromatography (hexanes:ethyl acetate, 20:1 to 5:1). R_f 0.45 (hexanes:ethyl acetate, 3:1); ^{1}H NMR (500 MHz, C_6D_6) δ 8.08 (d, *J* = 8.3 Hz, 2 H), 6.79 (d, *J* = 8.3 Hz, 2 H), 5.60 (dddd, *J* = 17.1, 10.3, 8.3, 5.8 Hz, 1 H), 4.90-4.84 (m, 2 H), 4.48 (ddd, *J* = 15.5, 5.0, 3.0 Hz, 1 H), 2.84 (ddd, *J* = 15.7, 9.8, 2.5 Hz, 1H), 2.39 (dtt, *J* = 14.1, 9.3, 1.5 Hz,1 H), 2.01-1.97 (m, 1 H), 1.89-1.83 (partially obscured m, 1 H), 1.83 (s, 3 H), 1.37-1.26 (m, 4 H), 0.92-0.86 (m, 2 H); ^{13}C NMR (125 MHz, C_6D_6) δ 175.1, 143.9, 138.0, 136.4, 129.2, 127.8, 116.9, 45.3, 45.1, 36.4, 28.9, 28.3, 21.1; IR (neat) 3071, 2933, 2859, 1700, 1348, 1107, 1037 cm^{-1}; LRMS (ESI) calcd for $C_{16}H_{21}NO_3SNa$ 330.1 ($M+Na^+$), found 330.1.

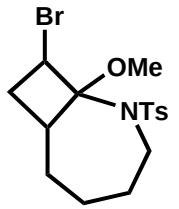


2. 83

4-methyl-N-(4-(2-oxocyclobutyl)butyl)benzenesulfonamide (2.83). The general cyclization protocol was carried out on lactam **2.18 (**10.0 mg, 0.0325 mmol) using $TiCl_4$ (0.116 mL, 1.06 mmol) in CH_2Cl_2 (9.5 mL), THF (0.56 mL, 6.39 mmol), TMEDA (0.95 mL, 6.39 mmol), activated Zn dust (154 mg, 2.37 mmol), $PbCl_2$ (35 mg, 0.126 mmol), and CH_3CHBr_2 (0.096 mL, 1.05 mmol) in CH_2Cl_2 (0.6 mL + 0.6 mL rinse) to give **2.82**. Because of its instability, **2.82** was characterized as the hydrolyzed product **2.83** as described below.

To a solution of the residue from the cyclization of **2.81** in ethyl acetate (3 mL) at 0 °C was added 1.0 M HCl (2 mL) . After the reaction mixture was allowed to warm to rt over 1 and the reaction was quenched with sat. $NaHCO_3$ (aq., 10 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The organic

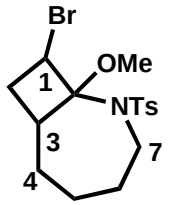
extracts were dried with $MgSO_4$ and concentrated. The resulting residue was purified by flash chromatography (hexanes:ethyl acetate, 10: to 5:1 to 2:1) to give ketone **2.83** (6.0 mg, 63% for two steps) as a colorless oil. R_f 0.17 (hexanes:ethyl acetate, 3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.2 Hz, 2 H), 7.29 (d, *J* = 7.9 Hz, 2 H), 4.32 (broad s, 1 H), 3.20 (broad s, 1 H), 3.04-2.96 (m, 1 H), 2.93-2.84 (m, 3 H), 2.41 (s, 3 H), 2.14 (ddd, *J* = 21.0, 10.3, 4.9 Hz, 1 H), 1.63-1.55 (m, 3 H), 1.47-1.23 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.8, 143.4, 137.0, 129.7, 127.1, 60.1, 44.5, 42.9, 29.4, 29.0, 24.0, 21.5, 16.8; IR (neat) 3425 (broad), 1769, 1643, 1324, 1157, 1091 cm^{-1}; LRMS (ESI) calcd for $C_{15}H_{21}NO_3SNa$ 318.1, ($M+Na^+$), found 318.1.



2. 84

(1S,7R,9S)-9-bromo-1-methoxy-2-tosyl-2-aza-bicyclo[5.2.0]nonane (2.84). To a solution containing crude **2.82** (0.072 mmol) in methanol (5 mL) at 0 °C was added NBS (20 mg, 0.11 mmol). The reaction mixture was stirred at 0 °C for 2 h at which time the reaction was quenched with sat. $NaHCO_3$ (aq., 2 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 20 mL), dried ($MgSO_4$) and concentrated. The resulting residue was purified by flash chromatography (hexanes:ethyl acetate, 10:1 to 5:1) to give diasteromers **2.84a** (10.9 mg, 39% for two steps) and **2.84b** (5.3 mg, 19% for 2 steps) as colorless oils. Data for isomer **2.84a**: R_f 0.53 (hexanes:ethyl acetate, 3:1); ^{1}H NMR (500 MHz, C_6D_6) δ 7.92 (d, *J* = 8.3 Hz, 2 H), 6.76 (d, *J* = 7.8 Hz, 2 H), 5.34 (dd, *J* = 9.6, 9.6 Hz, 1 H), 3.66-3.62 (m, 1 H), 3.17 (s, 3 H), 2.60 (ddd, *J* = 15.0, 12.5, 1.0 Hz, 1 H), 2.42-

2.36 (m, 1 H), 2.12-2.07 (m, 1 H), 1.85 (s, 3 H), 1.64-1.59 (m, 1 H), 1.47-1.11 (m, 4 H), 1.02-0.99 (m, 1 H), 0.77-0.68 (m, 1 H); ^{13}C NMR (125 MHz, C_6D_6) δ 142.9, 139.5, 129.4, 128.3, 128.2, 127.8, 94.7, 52.1, 48.4, 47.4, 47.2, 35.1, 32.0, 29.5, 29.0, 21.1; IR (neat) 2918, 2852, 1441, 1160, 1087, 1041 cm^{-1}; LRMS (ESI) calcd for $C_{18}H_{22}BrNO_3SNa$ 410.0 (M+Na$^+$); found 410.0, 412.0 (M+Na$^+$+2).



Summary of COSY spectrum for **2.84a**:

Proton at 5.34 ppm (H-1) shows crosspeaks with protons at 2.39 ppm (H-2) and 1.61 ppm (H-2')

Proton at 2.09 ppm (H-3) shows crosspeaks with protons at 2.39 ppm (H-2), 1.61 ppm (H-2') and 1.24 (H-4)

Proton at 3.64 ppm (H-7) shows crosspeaks with protons at 2.60 ppm (H-7') and 1.14 ppm (H-6)

Proton at 2.60 ppm (H-7') shows crosspeaks with protons at 3.64 ppm (H-7) and 1.42 ppm (H-6')

Data for isomer **2.84b**: R_f 0.48 (hexanes:ethyl acetate, 3:1); ^{1}H NMR (500 MHz, C_6D_6) δ 8.18 (d, *J* = 7.8 Hz, 2 H), 6.77 (d, *J* = 8.3 Hz, 2 H), 4.82 (dd, *J* = 5.4, 5.4 Hz, 1 H), 3.61 (d, *J* = 16.1 Hz, 1 H), 3.23 (s, 3 H), 2.82-2.75 (m, 1 H), 2.68 (ddd, *J* = 12.7, 8.8 Hz, 1 H), 2.55 (ddd, *J* = 13.3 Hz, 1 H), 2.17-2.10 (m, 1 H), 1.86 (s, 3 H), 1.69 (d, *J* = 12.7 Hz, 1 H), 1.46-1.35 (m, 2 H), 1.12-1.09 (m, 2 H), 0.76-0.68 (m, 1 H); ^{13}C NMR (125 MHz, C_6D_6) δ 143.0, 138.7, 129.3, 129.2, 128.3, 128.2, 127.8, 95.6, 52.0, 49.9, 48.1, 47.4, 36.4, 34.1,

29.98, 29.96, 21.1; IR (neat) 3056, 2927, 2854, 1443, 1342, 1264, 1162, 1088, 1045 cm^{-1}; LRMS (ESI) calcd for $C_{18}H_{22}BrNO_3SNa$ 410.0 ($M+Na^+$), found 410.0, 412.0 ($M+Na^+$+2).

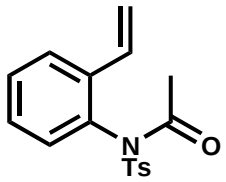
Summary of COSY spectrum for **2.84b**:

Proton at 4.82 ppm (H-1) shows crosspeak with proton at 2.68 ppm (H-2)

Proton at 2.55 ppm (H-3) shows crosspeaks with protons at 2.68 ppm (H-2), 2.13 ppm (H-4), and 1.46 (H-4')

Proton at 3.61 ppm (H-7) shows crosspeaks with protons at 2.79 ppm (H-7') and 1.11 ppm (H-6)

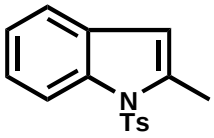
Proton at 2.79 ppm (H-7') shows crosspeaks with protons at 3.61 ppm (H-7) and 1.11 ppm (H-6)



2. 93

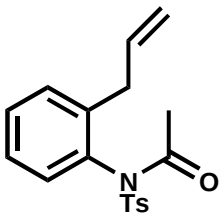
N-tosyl-N-(2-vinylphenyl)acetamide (2.93). Prepared according to the general procedure described above using N-(2-ethenylphenyl) acetamide[32] (80. mg, 0.50 mmol), NaH (26 mg of a 60% dispersion in mineral oil, 0.65 mmol), and tosyl chloride (124 mg, 0.650 mmol) to give 140 mg (89%) of N-tosyl protected amide **2.93** as a white waxy solid after flash chromatography (hexanes:ethyl acetate, 20:1 to 10:1). mp 73-74 °C; R_f 0.36 (hexanes:ethyl acetate, 3:1); ^{1}H NMR (500 MHz, C_6D_6) δ 8.16 (d, J = 8.3 Hz, 2 H), 7.34 (d, J = 7.8 Hz, 1 H), 7.00-6.91 (m, 4 H), 6.77 (d, J = 8.8 Hz, 2 H), 5.50 (d, J = 17.0 Hz, 1 H), 5.02 (d, J = 10.7 Hz, 1 H), 1.85 (s, 3 H), 1.38 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 169.4, 144.6, 138.2, 137.2, 135.5, 131.9, 130.6, 130.2, 129.9, 129.3, 129.0, 126.5,

117.9, 24.4, 21.2; IR (neat) 3066, 2921, 1709, 1423, 1167 cm^{-1}; LRMS (ESI) calcd for $C_{17}H_{17}NO_3SNa$ 338.1 ($M+Na^+$), found 338.1.



2. 94

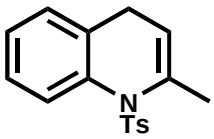
2-methyl-1-tosyl-1H-indole (2.94). The general cyclization protocol was carried out on amide **2.93** (17 mg, 0.054 mmol) using $TiCl_4$ (0.19 mL, 1.7 mmol) in CH_2Cl_2 (15.5 mL), THF (0.91 mL, 10. mmol), TMEDA (1.55 mL, 10.4 mmol), activated Zn dust (252 mg, 3.88 mmol), $PbCl_2$ (57 mg, 0.20 mmol), and CH_3CHBr_2 (0.157 mL, 1.72 mmol) in CH_2Cl_2 (1.0 mL + 1.0 mL rinse) to give 10.8 mg (70 %) of **2.94** as a waxy solid after flash chromatography (hexanes:ethyl acetate, 20:1 to 10:1 to 5:1). mp 65-67 °C; R_f 0.62 (hexanes:ethyl acetate, 3:1); ^{1}H NMR (500 MHz, C_6D_6) δ 8.50 (d, *J* = 8.3 Hz, 1 H), 7.50 (d, *J* = 8.3 Hz, 2 H), 7.19 (d, *J* = 7.8 Hz, 1 H), 7.11-7.10 (partially obscured m, 1 H), 7.02 (t, *J* = 7.6 Hz, 1 H), 6.38 (d, *J* = 7.8 Hz, 2 H), 5.91 (d, *J* = 0.98 Hz, 1 H), 2.40 (s, 3 H), 1.58 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 144.1, 137.2, 130.2, 129.7, 128.2, 127.8, 126.4, 124.1, 123.8, 120.3, 115.2, 109.9, 20.9, 15.7; IR (neat) 2921, 1596, 1449, 1367, 1172, 1091 cm^{-1}; LRMS (ESI) calcd for $C_{16}H_{15}NO_2SNa$ 308.1 ($M+Na^+$), found 308.1.



2. 95

N-(2-allylphenyl)-N-tosylacetamide (2.95). Prepared according to the general procedure described above using N–[2-(2-propen-1-yl)phenyl]- acetamide[33] (88 mg, 0.50

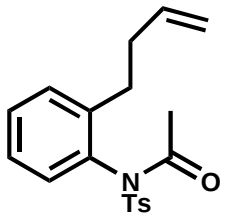
mmol), NaH (26 mg of a 60% dispersion in mineral oil, 0.65 mmol), and tosyl chloride (124 mg, 0.650 mmol) to give 140 mg (85%) of N-tosyl protected amide **2.95** as a colorless oil after flash chromatography (hexanes:ethyl acetate, 20:1 to 10:1). R_f 0.51 (CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 8.14 (d, *J* = 8.3 Hz, 2 H), 7.10 (d, *J* = 7.8 Hz, 1 H), 7.01 (dd, *J* = 7.7, 7.6 Hz, 1 H), 6.88 (ddd, *J* = 7.8, 7.8, 1.5 Hz, 1 H), 6.77-6.75 (m, 3 H), 5.77 (dddd, *J* = 17.6, 10.3, 7.8 Hz, 1 H), 5.08 (ddt, *J* = 17.1, 1.8, 1.8 Hz, 1 H), 4.96 (dd, *J* = 9.8, 0.9 Hz, 1 H), 3.59-3.46 (m, 2 H), 1.84 (s, 3 H), 1.40 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 169.4, 144.5, 141.2, 137.3, 136.8, 135.7, 131.0, 130.1, 129.9, 129.8, 129.3, 128.3, 127.5, 117.4, 36.1, 24.6, 21.1; IR (neat) 2923, 1708, 1360, 1167 cm^{-1}; LRMS (ESI) calcd for $C_{18}H_{19}NO_3SNa$ 352.1 ($M+Na^+$), found 352.1.



2. 96

2-methyl-1-tosyl-1,4-dihydroquinoline (2.96). The general cyclization protocol was carried out on amide **2.95** (20 mg, 0.061 mmol) using $TiCl_4$ (0.21 mL, 1.9 mmol) in CH_2Cl_2 (17.5 mL), THF (1.03 mL, 11.8 mmol), TMEDA (1.75 mL, 11.8 mmol), activated Zn dust (285 mg, 4.38 mmol), $PbCl_2$ (64 mg, 0.23 mmol), and CH_3CHBr_2 (0.18 mL, 1.97 mmol) in CH_2Cl_2 (1.2 mL + 1.2 mL rinse) to give 14 mg (78 %) of **2.96** as a colorless oil following flash chromatography (hexanes:ethyl acetate, 20:1 to 10:1 to 5:1). R_f 0.55 (CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 8.02 (d, *J* = 8.3 Hz, 1 H), 7.39 (d, *J* = 7.8 Hz, 2 H), 7.05 (t, *J* = 7.8 Hz, 1 H), 6.89 (dt, *J* = 7.4, 1.0 Hz, 1 H), 6.54 (d, *J* = 7.3 Hz, 1 H), 6.50 (d, *J* = 7.8 Hz, 2 H), 5.12-5.10 (m, 1 H), 2.32-2.31 (m, 3 H), 1.86 (brs , 2 H), 1.74 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 143.3, 138.7, 138.7, 135.5, 134.9, 129.1,

128.3, 127.8, 127.2, 126.7, 126.6, 120.7, 27.4, 22.6, 21.0; IR (neat) 3032, 2921, 2850, 1487, 1455, 1356, 1169, 1089 cm^{-1}; LRMS (ESI) calcd for $C_{17}H_{17}NO_2SNa$ 322.1 ($M+Na^+$), found 322.1.

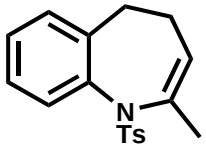


2. 97

N-(2-(but-3-enyl)phenyl)-N-tosylacetamide (2.97). To a solution of 2-(3-butenyl)aniline[13] (106 mg, 0.720 mmol) in CH_2Cl_2 (4.0 mL) at 0 °C was added pyridine (0.064 mL, 0.79 mmol) followed by a solution of acetyl chloride (0.065 mL, 0.79 mmol) in CH_2Cl_2 (1.5 mL). After 12 h, the mixture was quenched with sat. NH_4Cl (aq., 5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL), dried ($MgSO_4$) and concentrated. The resulting residue containing the acetamide corresponding to 2-(3-butenyl)aniline was taken on to the next step without additional purification.

The tosyl amide **2.97** was prepared according the general procedure using the acetamide from above, NaH (26 mg of a 60% dispersion in mineral oil, 0.65 mmol), and tosyl chloride (124 mg, 0.650 mol) to give 136 mg (55% over two steps) of N-tosyl protected amide **2.97** as a colorless oil after flash chromatography (hexanes:ethyl acetate, 20:1 to 10:1). R_f 0.43 (hexanes:ethyl acetate, 3:1); ^{1}H NMR (500 MHz, C_6D_6) δ 8.14 (d, J = 8.3 Hz, 2 H), 7.06-7.01(m, 2 H), 6.90-6.86 (m, 1 H), 6.79 (d, J = 7.8 Hz, 1 H), 6.77 (d, J = 7.9 Hz, 2 H), 5.74 (ddt, J = 17.1, 10.3, 6.3 Hz, 1 H), 5.04 (ddd, J = 17.1, 1.8, 1.8 Hz, 1 H), 4.94 (dd, J = 9.8, 1.0 Hz, 1 H), 2.96-2.90 (m, 1 H), 2.78-2.72 (m, 1 H), 2.44-2.41 (m, 1 H), 2.33-2.25 (m, 1 H), 1.85 (s, 3 H), 1.40 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6)

δ 169.4, 144.5, 142.6, 137.8, 137.4, 136.8, 130.4, 130.1, 129.8, 129.8, 129.3, 127.2, 115.6, 33.7, 30.6, 24.4, 21.1; IR (neat) 3072, 2925, 1708, 1362, 1167 cm^{-1}; LRMS (ESI) calcd for $C_{19}H_{21}NO_3SNa$ 366.1 ($M+Na^+$), found 366.1.

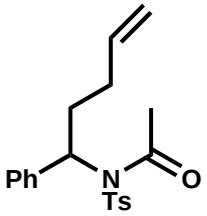


2. 98

(Z)-2-methyl-1-tosyl-4,5-dihydro-1H-benzo[b]azepine (2.98). The general cyclization protocol was carried out on amide **2.97** (35 mg, 0.10 mmol) using $TiCl_4$ (0.37 mL, 3.4 mmol) in CH_2Cl_2 (31 mL), THF (1.82 mL, 20.8 mmol), TMEDA (3.10 mL, 20.8 mmol), activated Zn dust (504 mg, 7.75 mmol), $PbCl_2$ (110 mg, 0.41 mmol), and CH_3CHBr_2 (0.31 mL, 3.4 mmol) in CH_2Cl_2 (2.0 mL + 2.0 mL rinse) to give 18 mg (58 %) of **2.98** and 6.8 mg (18%) of acyclic enamine **2.99** as colorless oils following flash chromatography (hexanes:ethyl acetate, 20:1 to 10:1 to 5:1). Data for **2.98**: R_f 0.62 (hexanes:ethyl acetate, 3:1); ^1H NMR (500 MHz, C_6D_6) δ 7.70 (d, *J* = 8.3 Hz, 2 H), 7.29 (dd, *J* = 7.8, 1.5 Hz, 1 H), 6.94 (dt, *J* = 7.2, 1.4 Hz, 1 H), 6.91 (t, *J* = 7.6, 2.0 Hz, 1 H), 6.79 (dd, *J* = 7.32, 1.5 Hz, 1 H), 6.65 (d, *J* = 7.8 Hz, 2 H), 4.79 (t, *J* = 3.5 Hz, 1 H), 2.88 (dt, *J* = 14.7, 5.4 Hz, 1 H), 2.30-2.29 (m, 3 H), 1.97-1.90 (m, 2 H), 1.81 (s, 3 H), 1.66-1.58 (m, 1 H); ^{13}C NMR (125 MHz, C_6D_6) δ 142.9, 142.4, 141.2, 138.8, 135.8, 129.5, 129.4, 129.2, 128.6, 127.8, 126.8, 121.8, 29.2, 28.0, 25.5, 21.1; IR (neat) 2922, 1487, 1453, 1346, 1162, 1091 cm^{-1}; LRMS (ESI) calcd for $C_{18}H_{19}NO_2SNa$ 336.1 ($M+Na^+$), found 336.1.

Acyclic enamine **2.99**: R_f 0.67 (hexanes:ethyl acetate, 3:1); ^1H NMR (500 MHz, C_6D_6) δ 7.80 (d, *J* = 8.3 Hz, 2 H), 7.11-6.86 (m, 8 H), 6.72 (d, *J* = 8.3 Hz, 2 H), 5.78-5.74

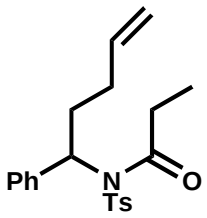
(m, 1 H), 5.52-5.45 (m, 2 H), 3.0-2.77 (m, 3 H), 2.38 (m, 2 H), 2.0 (m, 3 H), 1.87-1.84 (m, 6 H), 1.69 (m, 6 H), 1.61-1.56 (m, 6 H), 1.37-1.32 (m, 16 H), 0.99-0.90 (m, 5 H); IR (neat) 3057, 2920, 2851, 1712, 1350, 1265, 1160, 1092 cm^{-1}; LRMS (ESI) calcd for $C_{22}H_{27}NO_2SNa$ 392.2 ($M+Na^+$), found 392.3.



2.107

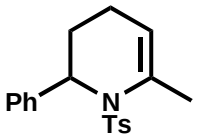
N-(1-phenylpent-4-enyl)-N-tosylacetamide (2.107). To a mixture of NaH (32 mg of a 60% dispersion in mineral oil, 0.79 mmol) in THF (2 ml) at 0 °C was added 4-methyl-N-(1-phenylpent-4-enyl)benzenesulfonamide (50 mg, 0.16 mmol). After stirring for 1 h, acetyl chloride (0.034 mL, 0.47 mmol) was added directly to the reaction mixture. The ice bath was removed and the reaction mixture was warmed to rt at which time the reaction was quenched with sat. NH_4Cl (aq., 5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL), dried ($MgSO_4$) and concentrated. The resulting residue was purified by flash chromatography (hexanes:ethyl acetate, 20:1 to 5:1) to give amide **2.107** (51 mg, 90%) as a colorless oil. R_f 0.50 (hexanes:ethyl acetate, 5:1); ^{1}H NMR (500 MHz, C_6D_6) δ 7.56 (d, *J* = 7.33 Hz, 2 H), 7.38 (d, *J* = 8.3 Hz, 2 H), 7.15-7.05 (m, 3 H), 6.59 (d, *J* = 8.3 Hz, 2 H), 5.85 (t, *J* = 7.81 Hz, 1 H), 5.71 (dddd, *J* = 17.1, 10.3, 6.8 Hz, 1 H), 4.99-4.94 (m, 2 H), 2.56-2.49 (m, 1 H), 2.46-2.39 (m, 1 H), 2.13-2.08 (m, 2 H), 2.07 (s, 3 H), 1.79 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 170.2, 144.1, 139.3, 137.9, 137.7, 129.5, 129.5, 128.4, 128.2, 127.8, 115.6, 61.2, 31.9, 31.7, 26.0, 21.0; IR (neat) 3066, 2930,

1770, 1698, 1356, 1237, 1166, 1089 cm^{-1}; LRMS (ESI) calcd for $C_{20}H_{23}NO_3SNa$ 380.1 ($M+Na^+$), found 380.1.



2.108

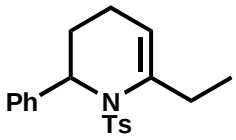
N-(1-phenylpent-4-enyl)-N-tosylpropionamide (2.108). Prepared according to the procedure described above for the preparation of **2.107** using 4-methyl-N-(1-phenylpent-4-enyl)benzenesulfonamide (50 mg, 0.16 mmol), NaH (32 mg of a 60% dispersion in mineral oil, 0.79 mmol), and propionyl chloride (0.041 mL, 0.47 mmol) to give 51.6 mg (88%) of N-tosyl protected amide **2.108** as a colorless oil after flash chromatography (hexanes:ethyl acetate, 20:1 to 5:1). R_f 0.50 (hexanes:ethyl acetate, 5:1); ^{1}H NMR (500 MHz, C_6D_6) δ 7.56 (d, *J* = 7.3 Hz, 2 H), 7.42 (d, *J* = 8.3 Hz, 2 H), 7.11-7.08 (m, 2 H), 7.05-7.03 (m, 1 H), 6.55 (d, *J* = 8.3 Hz, 2 H), 5.84 (dd, *J* = 7.8, 7.8 Hz, 1 H), 5.69 (dddd, *J* = 17.1, 10.2, 6.8, 6.8 Hz, 1 H), 4.97-4.91 (m, 2 H), 2.55-2.37 (m, 4 H), 2.15-2.04 (m, 2 H), 1.73 (s, 3 H), 0.83 (t, *J* = 7.08 Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 174.1, 144.1, 139.5, 138.2, 137.7, 129.5, 129.4, 129.2, 128.5, 128.5, 128.3, 128.2, 115.6, 61.2, 32.1, 31.8, 31.2, 21.0, 9.2; IR (neat) 3066, 2981, 2940, 1761, 1700, 1353, 1162, 1086 cm^{-1}; LRMS (ESI) calcd for $C_{21}H_{25}NO_3SNa$ 394.2 ($M+Na^+$), found 394.2.



2.109

6-methyl-2-phenyl-1-tosyl-1,2,3,4-tetrahydropyridine (2.109). The general cyclization protocol was carried out on amide **2.107** (30. mg, 0.084 mmol) using $TiCl_4$ (0.29 mL, 2.65 mmol) in CH_2Cl_2 (24.0 mL), THF (1.42 mL, 16.2 mmol), TMEDA (2.41 mL, 16.2 mmol), activated Zn dust (392 mg, 6.03 mmol), $PbCl_2$ (88 mg, 0.32 mmol), and CH_3CHBr_2 (0.24 mL, 2.63 mmol) in CH_2Cl_2 (1.5 mL + 1.5 mL rinse) to give 16.5 mg (60 %) of **2.109** and 6.4 mg (20%) of the corresponding acyclic enamine **2.110** as colorless oils after flash chromatography (hexanes:ethyl acetate, 20:1 to 10:1 to 5:1). Data for **2.109**: R_f 0.56 (hexanes:ethyl acetate, 5:1); ^{1}H NMR (500 MHz, C_6D_6) δ 7.71 (d, *J* = 8.3 Hz, 2 H), 7.24 (dd, J = 6.8, 1.0 Hz, 2 H), 7.12 (partially obscured t, *J* = 7.8 Hz, 1 H), 7.04 (t, *J* = 7.4 Hz, 1 H), 6.71 (d, *J* = 8.3 Hz, 2 H), 5.68 (broad s, 1 H), 4.60 (broad s, 1 H), 2.31 (d, *J* = 1.0 Hz, 3 H), 1.83 (s, 3 H), 1.71-1.69 (m, 1 H), 1.43-1.35 (m, 4 H); ^{13}C NMR (125 MHz, C_6D_6) δ 142.9, 140.3, 138.7, 133.1, 129.6, 128.6, 128.3, 127.8, 127.5, 127.0, 126.3, 113.7, 57.6, 24.6, 23.9, 21.1, 19.2; IR (neat) 2921, 1450, 1344, 1164, 1092 cm^{-1}; LRMS (ESI) calcd for $C_{19}H_{21}NO_2SNa$ 350.1 ($M+Na^+$), found 350.1.

Acyclic enamide **2.110**: R_f 0.66 (hexanes:ethyl acetate, 5:1); ^{1}H NMR (500 MHz, C_6D_6) δ 7.85-7.82 (m,2 H), 7.26-7.25 (m, 2 H), 7.0-7.0 (m, 4 H), 6.75 (m, 2 H), 5.48-5.28 (m, 2 H), 4.94-4.88 (m, 1 H), 1.93 (m, 2 H), 1.86 (s, 3 H), 1.83-1.78 (m, 2 H), 1.64-1.56 (m, 2 H), 1.53 (s, 3 H), 1.35-1.32 (m, 2 H), 1.26-1.17 (m, 5 H), 0.91 (m, 1 H), 0.81 (m, 3 H); IR (neat) 2928, 1338, 1160, 1092 cm^{-1}; LRMS (ESI) calcd for $C_{22}H_{29}NO_2SNa$ 406.2 ($M+Na^+$), found 406.2.

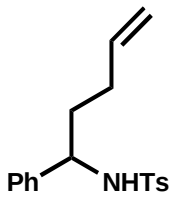


2.111

6-ethyl-2-phenyl-1-tosyl-1,2,3,4-tetrahydropyridine (2.111). The general cyclization protocol was carried out on amide **2.108** (25 mg, 0.067 mmol) using $TiCl_4$ (0.23 mL, 2.1 mmol) in CH_2Cl_2 (19 mL), THF (1.13 mL, 12.8 mmol), TMEDA (1.92 mL, 12.8 mmol), activated Zn dust (310 mg, 4.8 mmol), $PbCl_2$ (70.8 mg, 0.255 mmol), and CH_3CHBr_2 (0.195 mL, 2.14 mmol) in CH_2Cl_2 (1.2 mL + 1.2 mL rinse) to give 13.8 mg (60 %) of **2.111** and 5.3 mg (20%) of the corresponding acyclic enamide **2.112** as colorless oils after flash chromatography (hexanes:ethyl acetate, 20:1 to 10:1 to 5:1). Data for **2.111**: R_f 0.63 (hexanes:ethylacetate, 3:1); ^{1}H NMR (500 MHz, C_6D_6) δ 7.74 (d, *J* = 8.3 Hz, 2 H), 7.33 (d, *J* = 8.3 Hz, 2 H), 7.14 (partially obscured t, *J* = 7.8 Hz, 2 H), 7.05 (t, *J* = 7.3 Hz, 1 H), 6.73 (d, *J* = 8.3 Hz, 2 H), 5.58 (broad d, *J* = 3.4 Hz, 1 H), 4.77 (broad s, 1 H), 3.03 (dq, *J* 14.6, 7.3 Hz, 1 H), 2.57 (dq, *J* = 14.6, 7.3 Hz, 1 H), 1.83 (s, 3 H), 1.71-1.67 (m, 1 H), 1.57-1.50 (m, 1 H), 1.40-1.33 (m, 2 H), 1.14 (t, *J* = 7.3 Hz, 3 H); ^{13}CNMR (125 MHz, C_6D_6) δ 142.9, 140.2, 139.0, 138.3, 129.6, 128.5, 128.3, 127.6, 127.1, 126.7, 113.4, 57.2, 30.0, 23.7, 21.1, 19.2, 13.3; IR (neat) 2924, 1451, 1345, 1166, 1092, 1022 cm^{-1}; LRMS (ESI) calcd for $C_{20}H_{23}NO_2SNa$ 364.1 ($M+Na^+$), found 364.1.

Acyclic enamide **2.112**: R_f 0.66 (hexanes:ethyl acetate, 3:1); ^{1}H NMR (500 MHz, C_6D_6) δ 7.87-7.83 (m,2 H), 7.31-7.18 (m, 3 H), 7.06-7.0 (m, 5 H), 6.78 (m, 2 H), 5.40-5.25 (m, 3 H), 5.01-4.92 (m, 1 H), 2.28-2.15 (m, 1H), 2.09-1.96 (m, 3 H), 1.88 (m, 7 H), 1.81 (s, 2 H), 1.65 (m, 1 H), 1.56 (d, *J* = 5.86 Hz, 3 H), 1.36-1.30 (m, 5 H), 1.09 (m, 1 H),

1.02-0.98 (m, 3 H), 0.80 (t, J = 7.33 Hz, 1 H); IR (neat) 2934, 1454, 1339, 1160, 1092, 1005, 703, 667 cm^{-1}; LRMS (ESI) calcd for $C_{24}H_{31}NO_2SNa$ 420.2 ($M+Na^+$), found 420.2.



2.113

4-methyl-N-(1-phenylpent-4-enyl)benzenesulfonamide (2.113). 3-butenylmagnesium bromide[34] (3.8 mL, 0.80 mol/L) was added dropwise to a solution of N-benzylidenebenzenesulfonamide[35] (259 mg, 1.00 mmol) in THF (1.0 mL) at -78°C. The reaction mixture was warmed to rt over 1 h after which time the reaction was quenched with sat. NH_4Cl (aq., 5 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The organic extracts were dried ($MgSO_4$) and concentrated. The resulting residue was purified by flash chromatography (hexanes:ethyl acetate, 10:1 to 3:1) to give **2.113** (246 mg, 78%) as a colorless solid. mp 66-68 °C; R_f 0.40 (hexanes:ethyl acetate, 3:1); ^{1}H NMR (500 MHz, C_6D_6) δ 7.74 (d, J = 8.3, 2 H), 7.00-6.98 (m, 2 H), 6.94-6.88 (m, 3 H), 6.67 (d, J = 8.3, 2 H), 6.43 (d, J = 8.3 Hz, 1 H), 5.63-5.55 (m, 1 H), 4.91-4.87 (m, 2 H), 4.45 (ddd, J = 7.3, 7.3, 7.3 Hz, 1 H), 1.95-1.82 (m, 3 H), 1.85 (s, 3 H), 1.70-1.61 (m, 1 H); ^{13}C NMR (125 MHz, C_6D_6) δ 142.5, 141.6, 139.0, 137.6, 129.4, 128.5, 127.4, 127.2, 127.0, 115.4, 58.1, 37.2, 30.4, 21.0; IR (neat) 3276 (broad), 3064, 2924, 1641, 1599, 1453, 1323, 1158, 1092 cm^{-1}; LRMS (ESI) calcd for $C_{18}H_{21}NO_2SNa$ 338.1 ($M+Na^+$), found 338.1.

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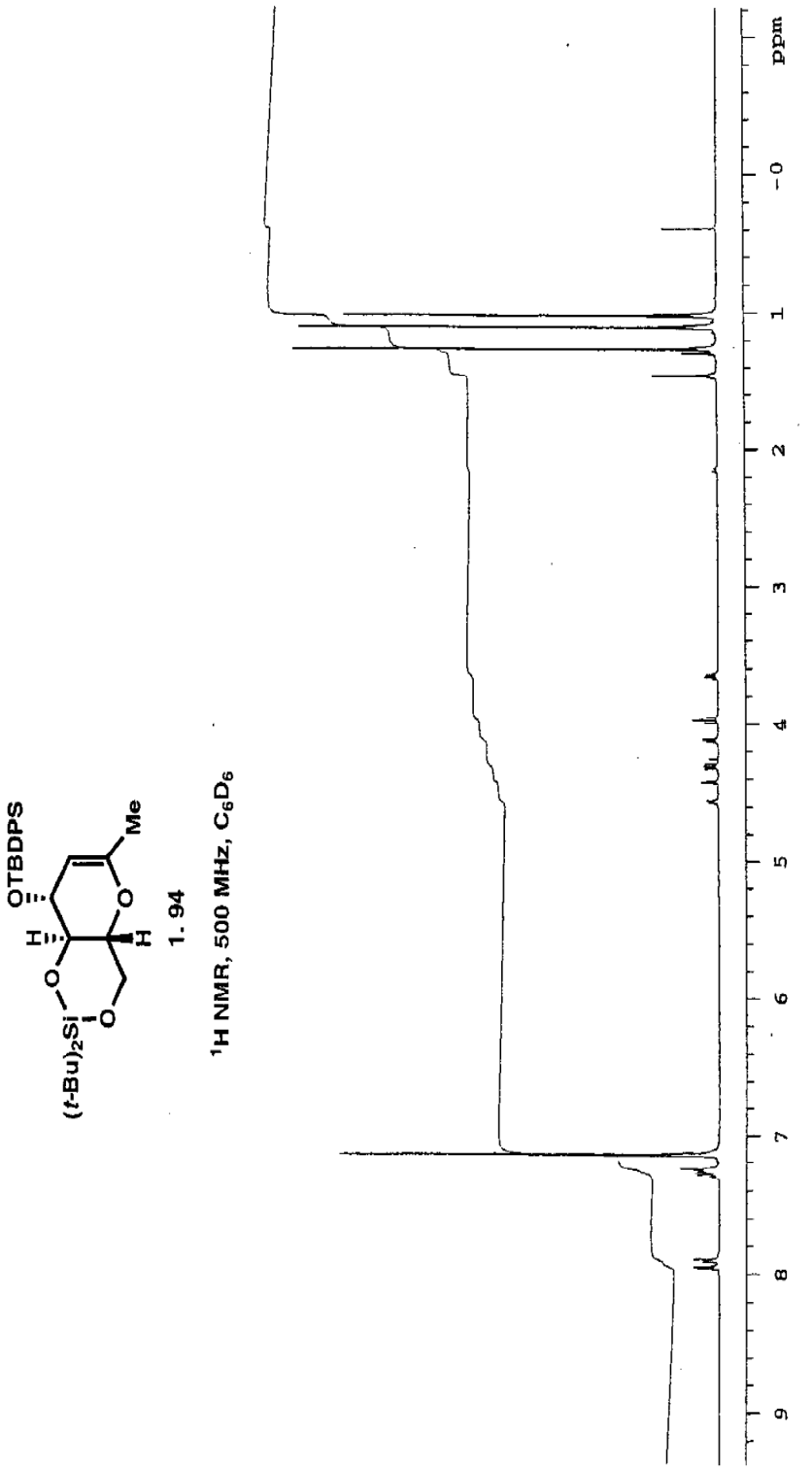
APPENDIX

^{1}H AND ^{13}C NMR SPECTRA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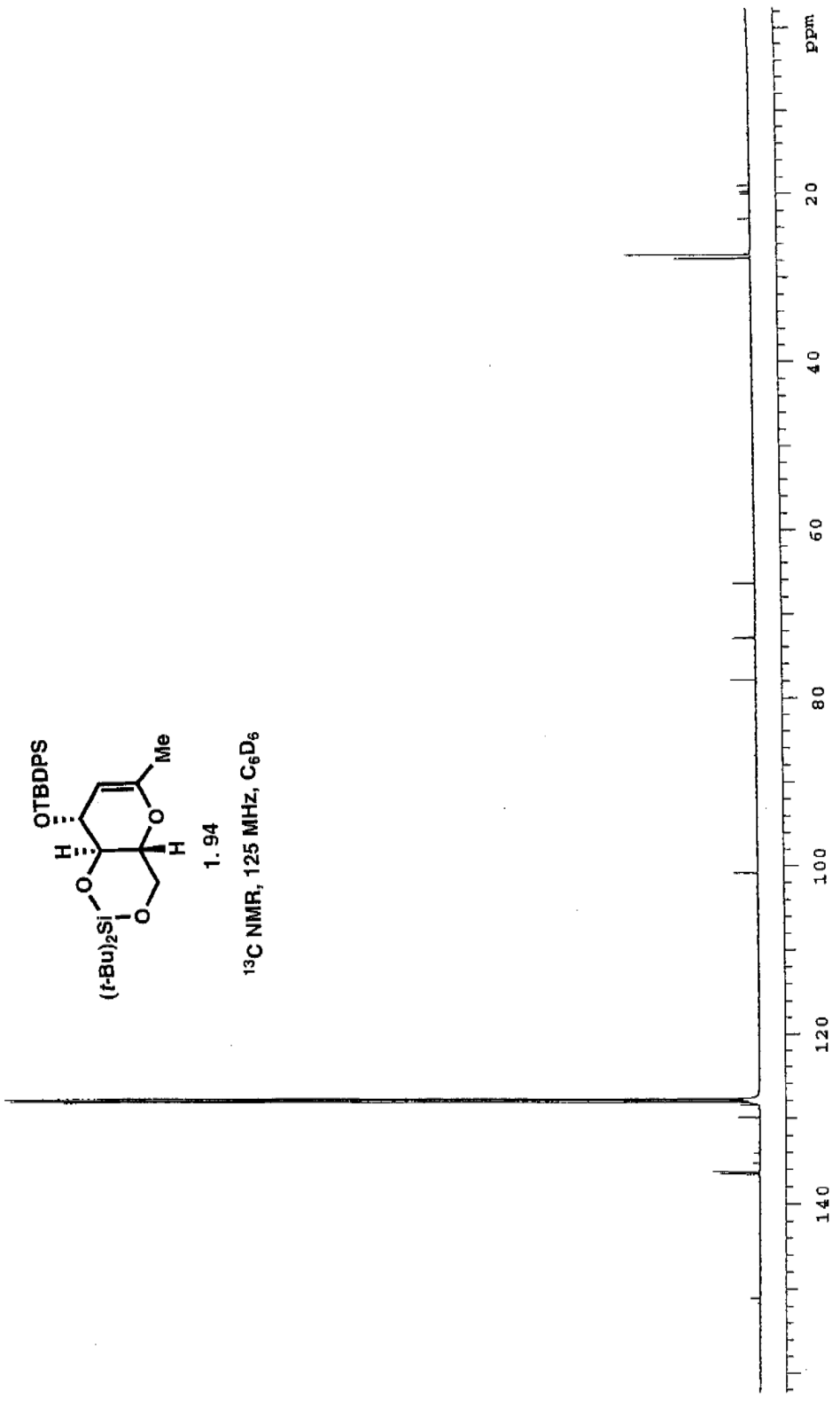
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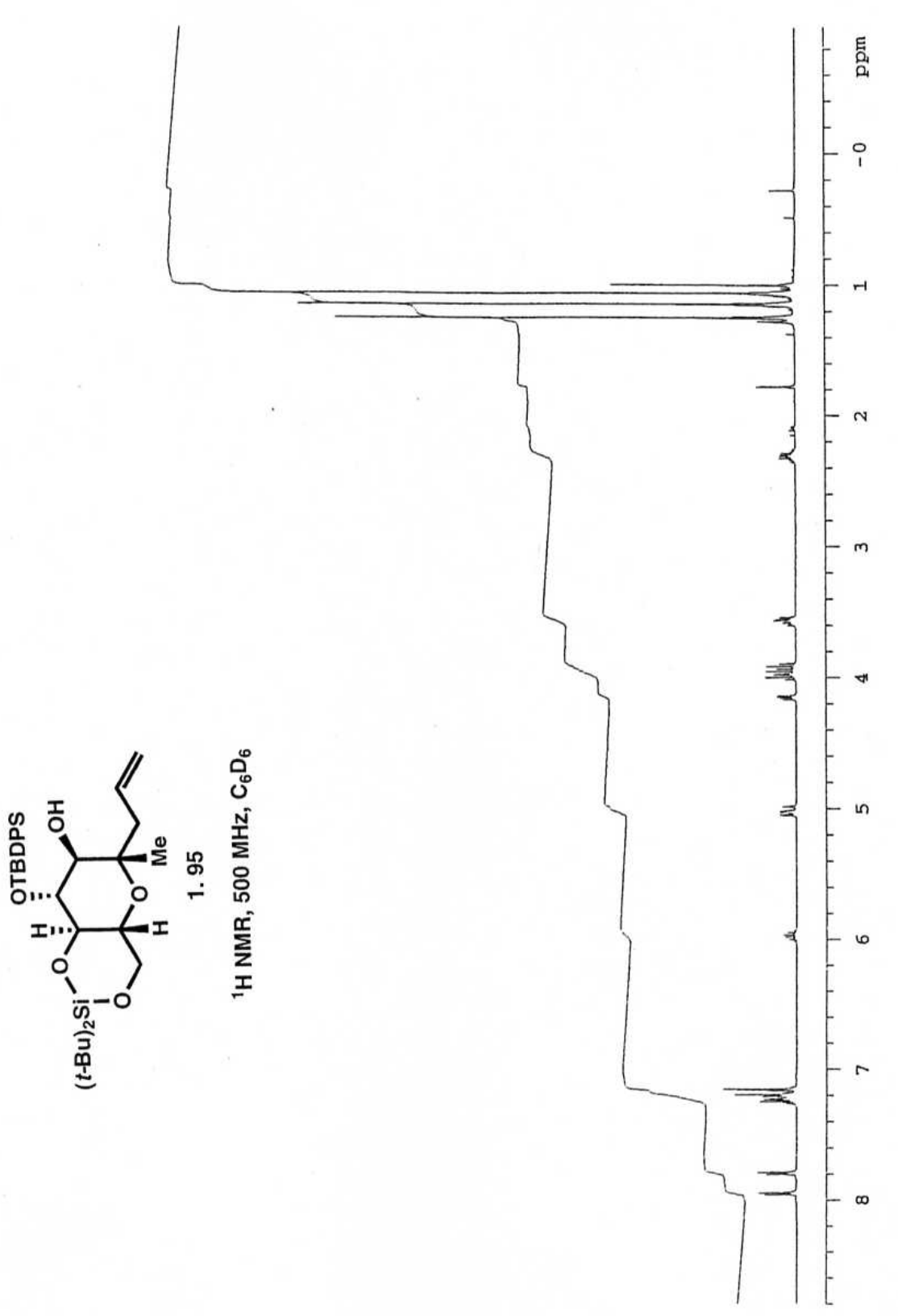
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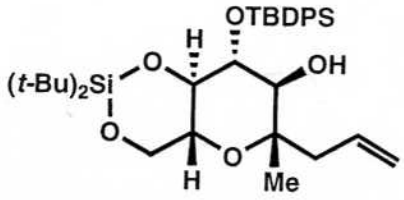

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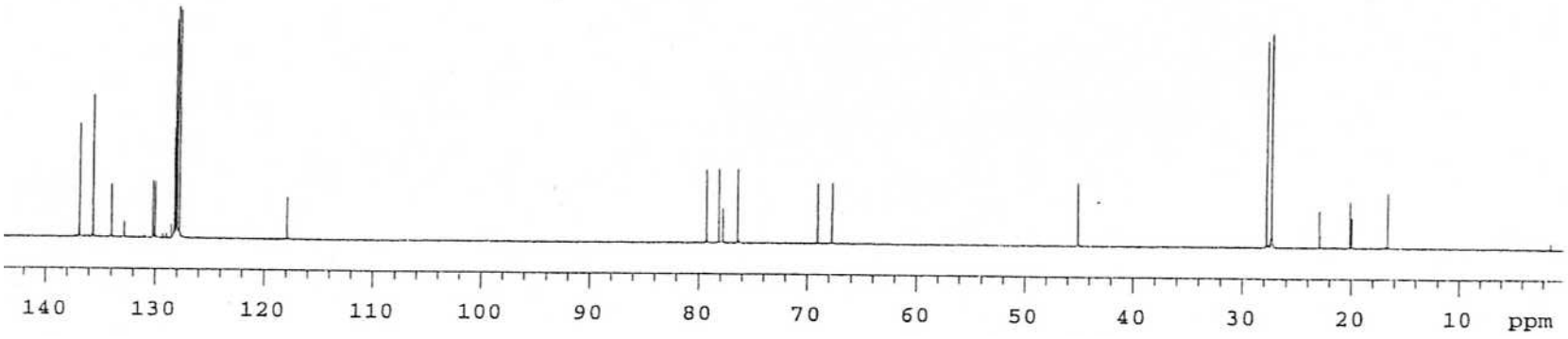

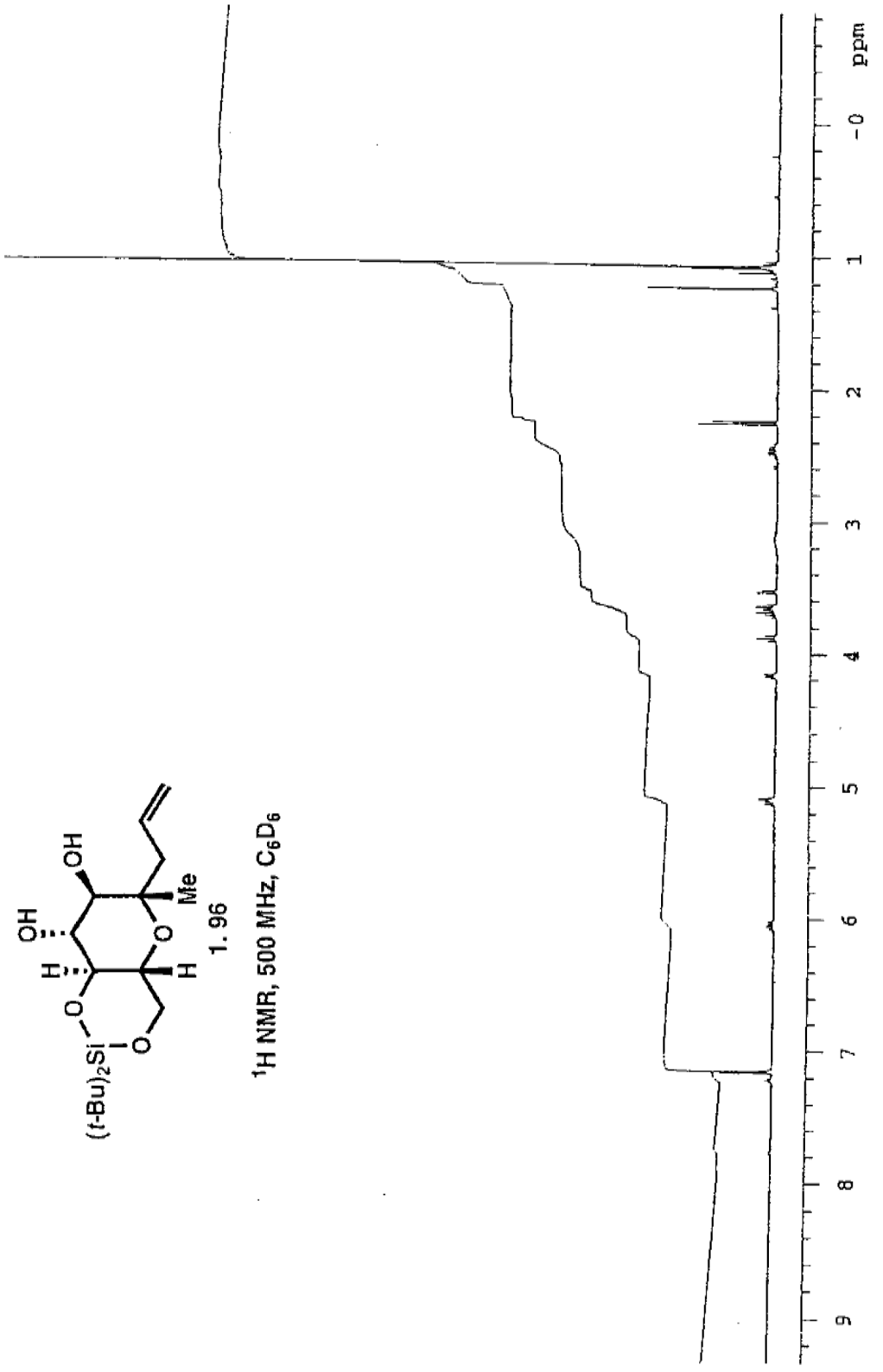
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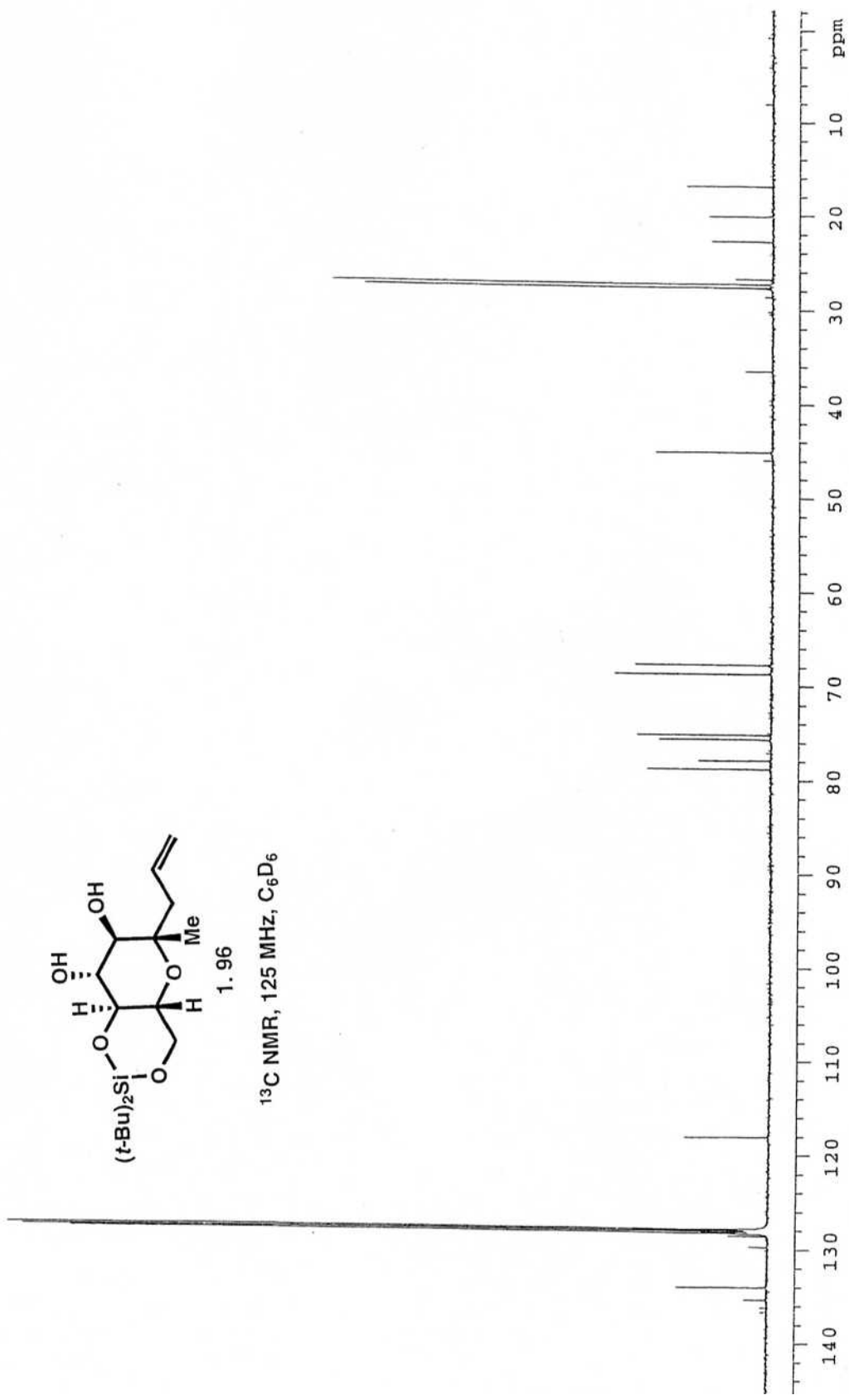
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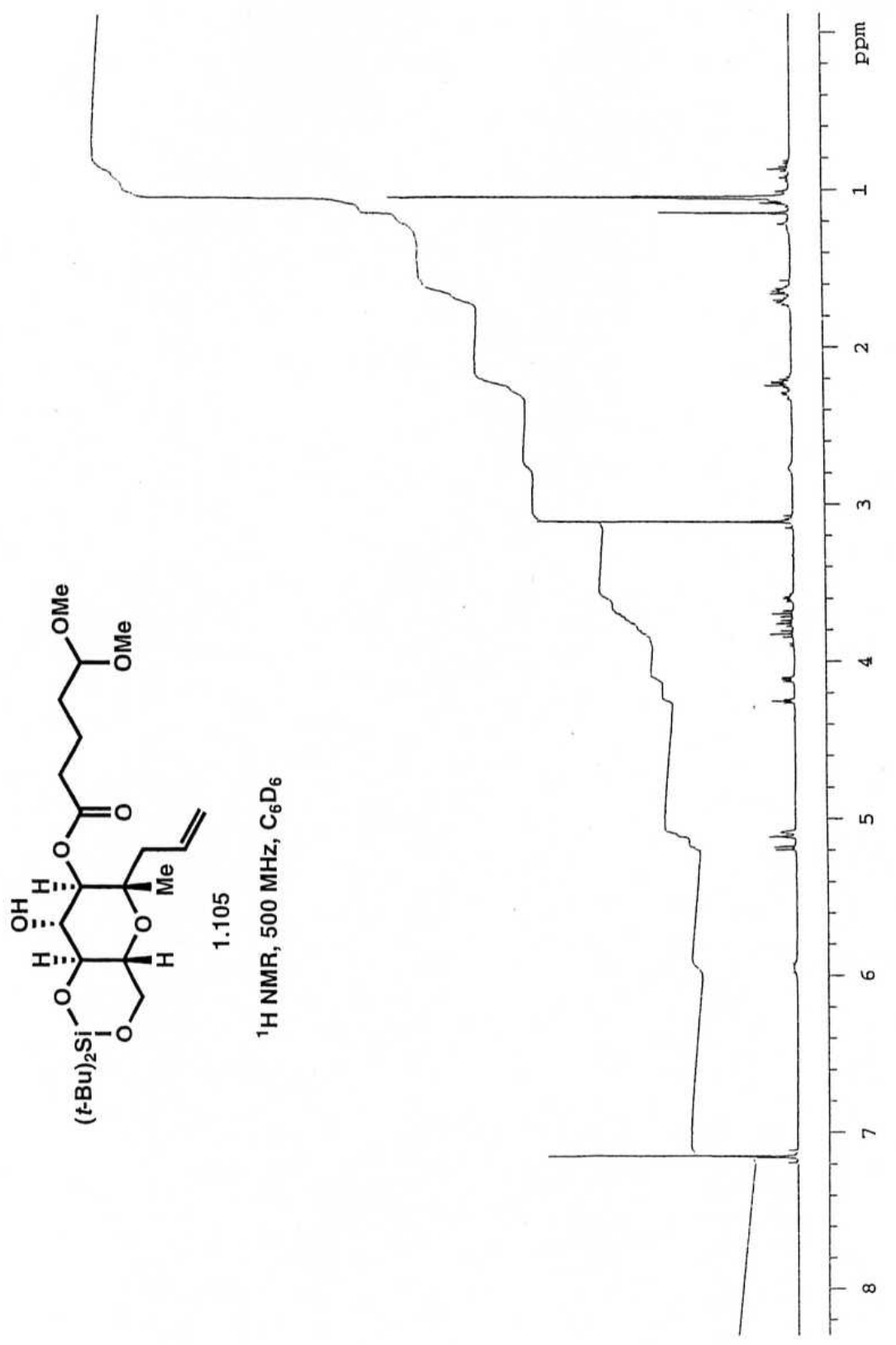

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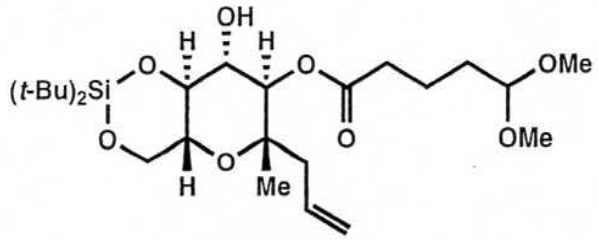

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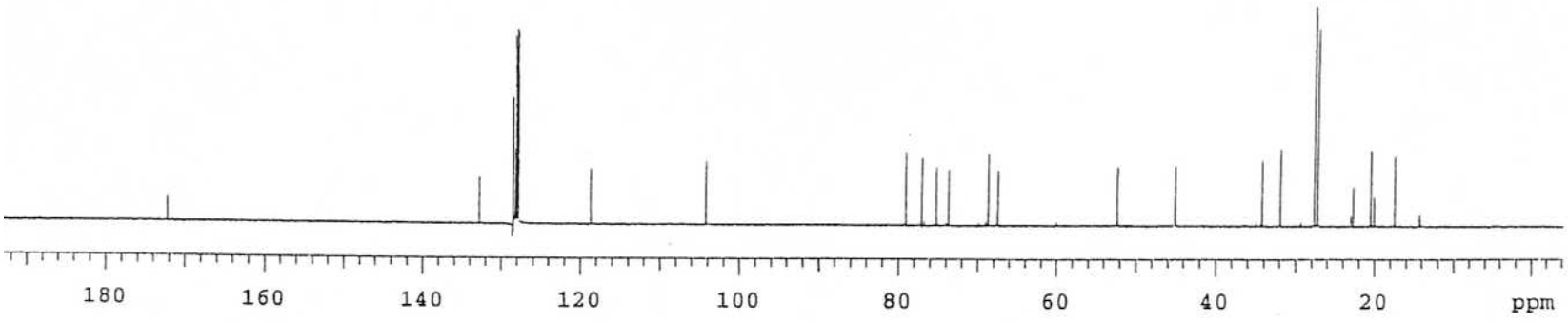

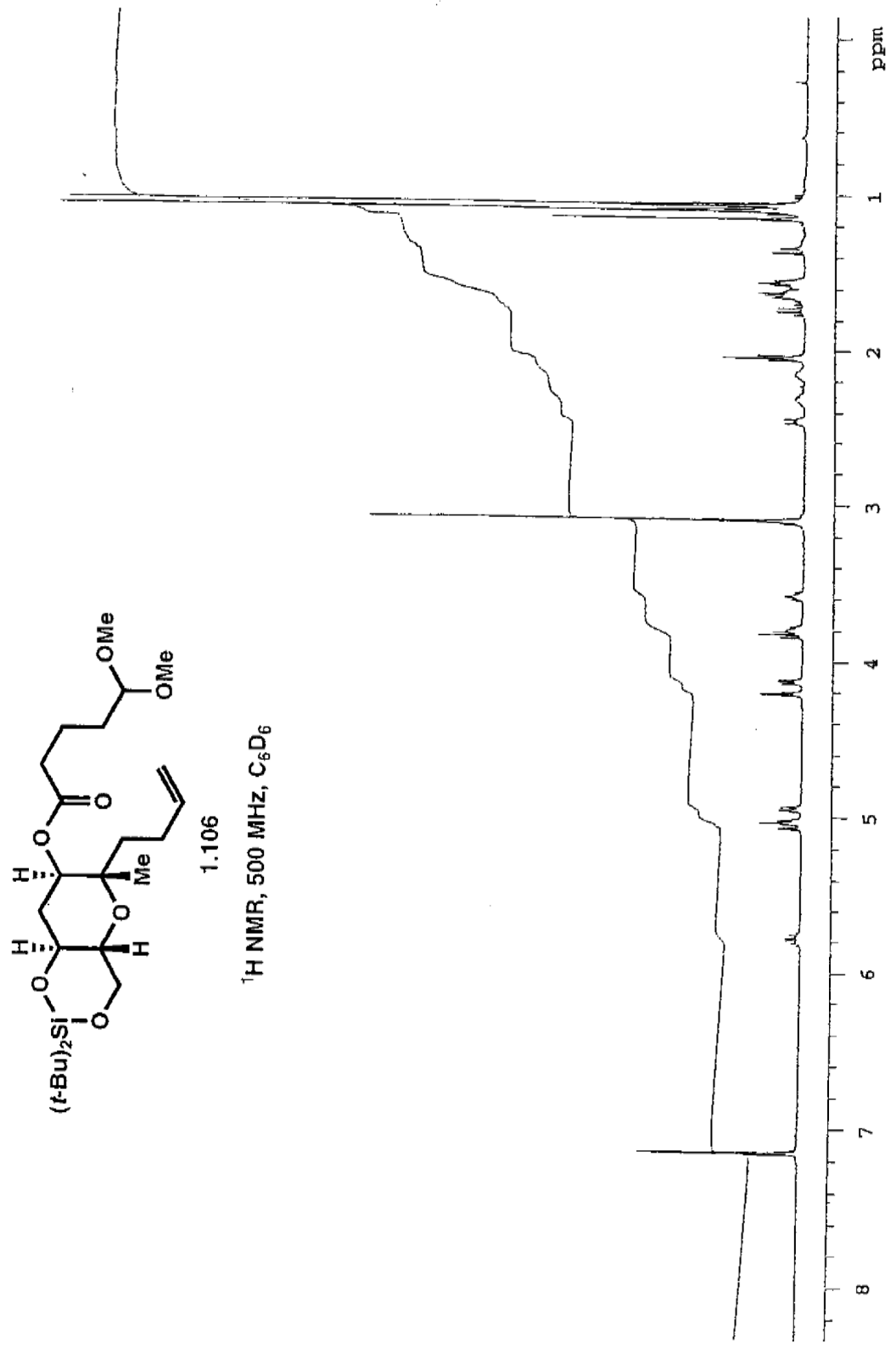

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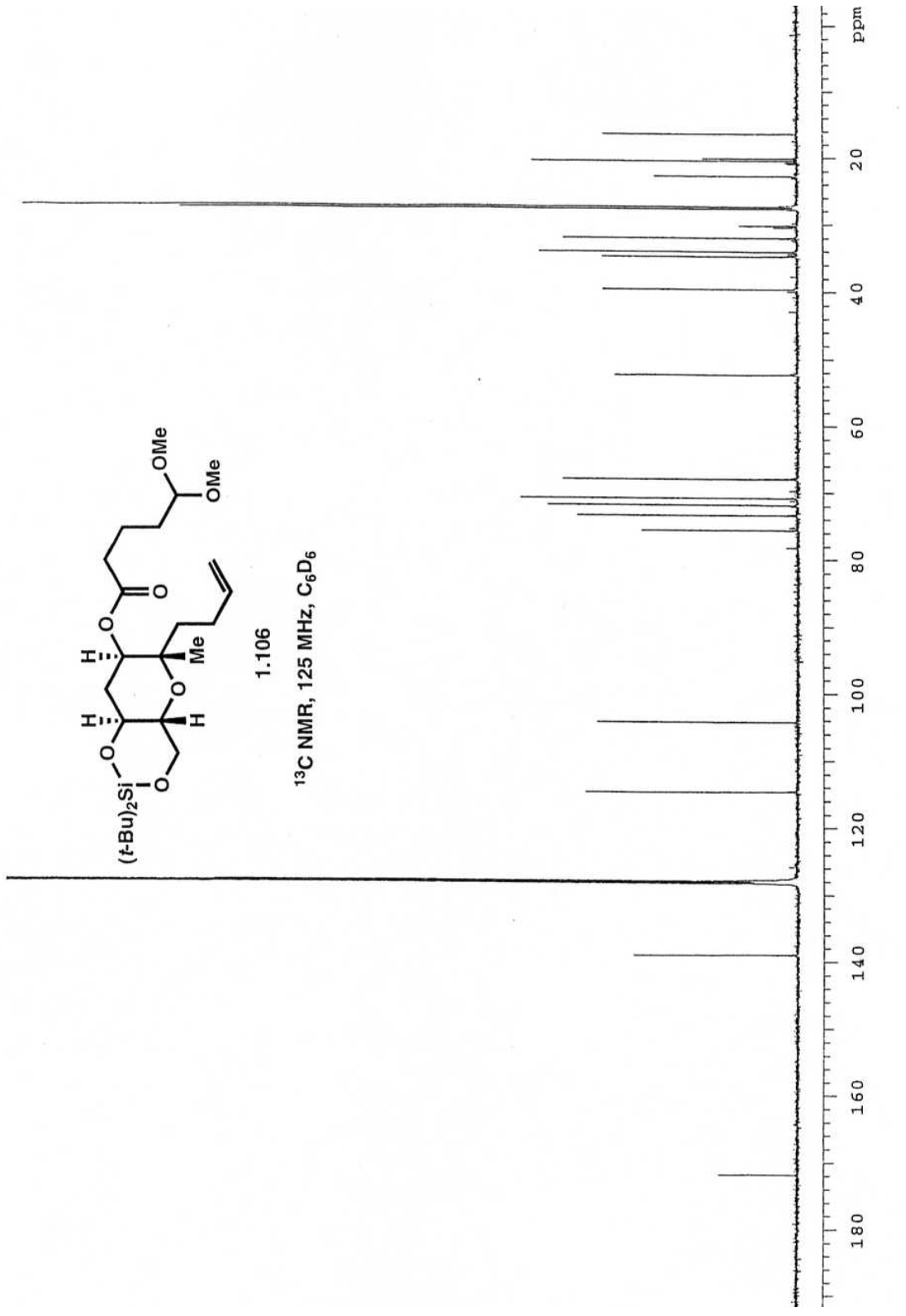
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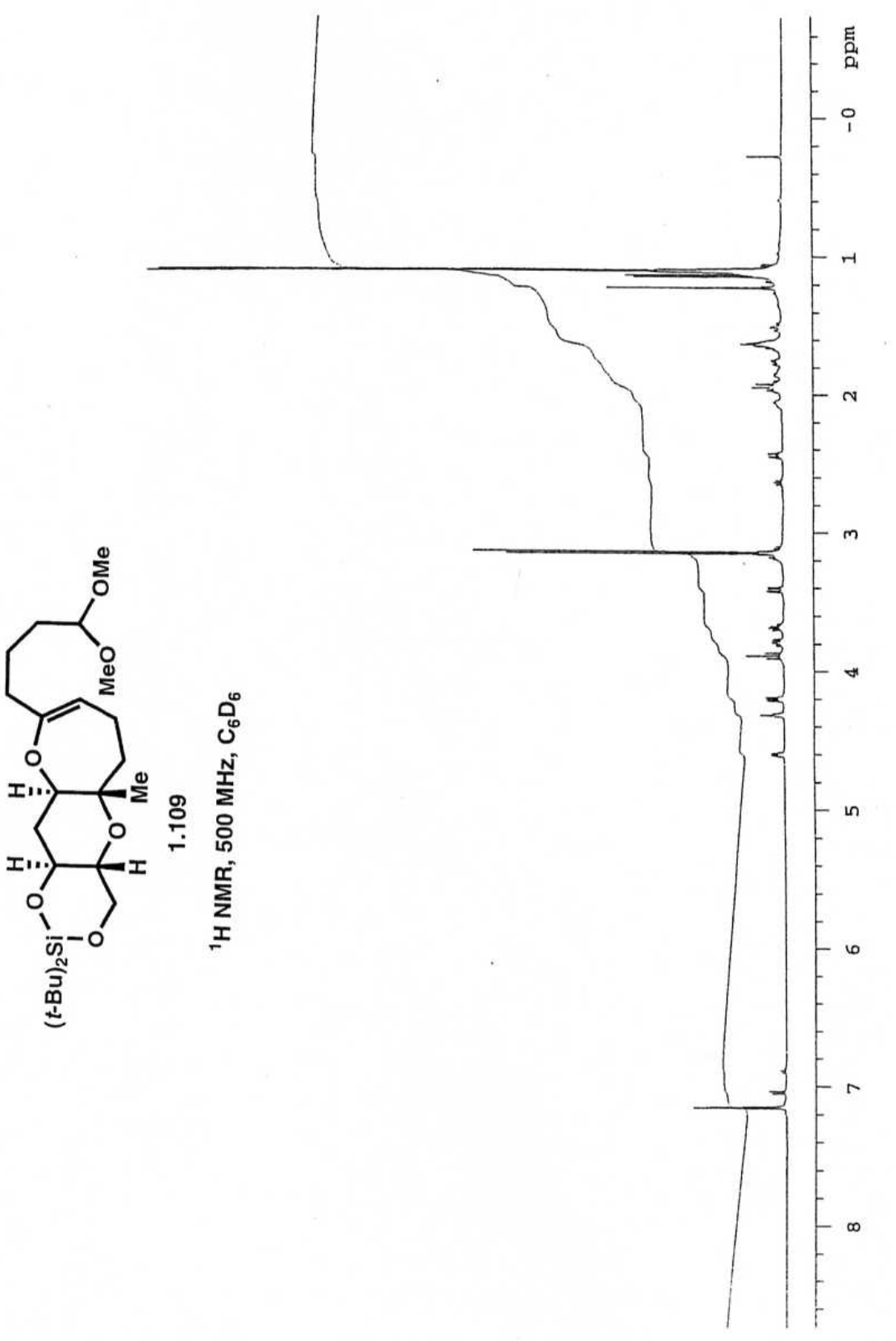

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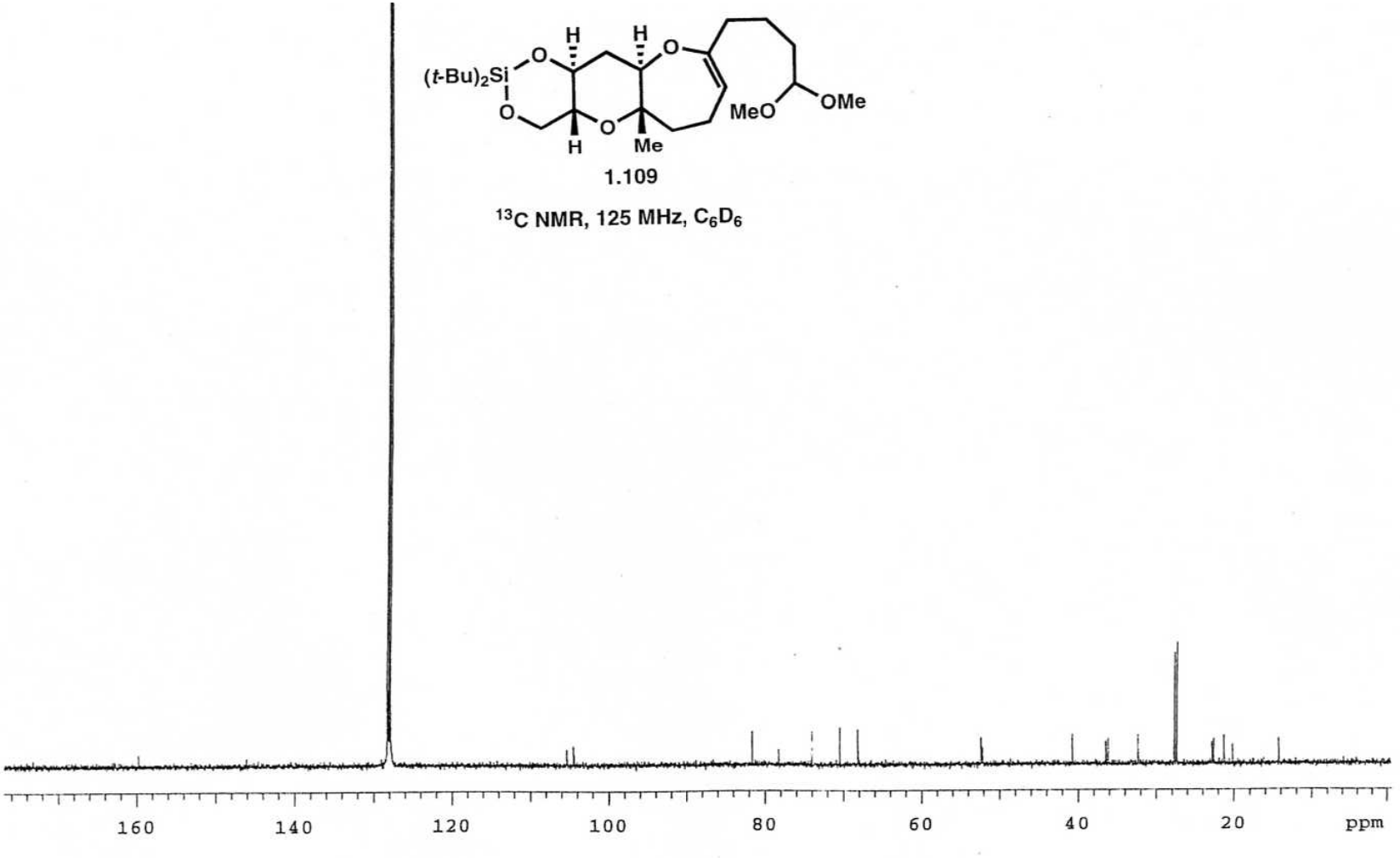

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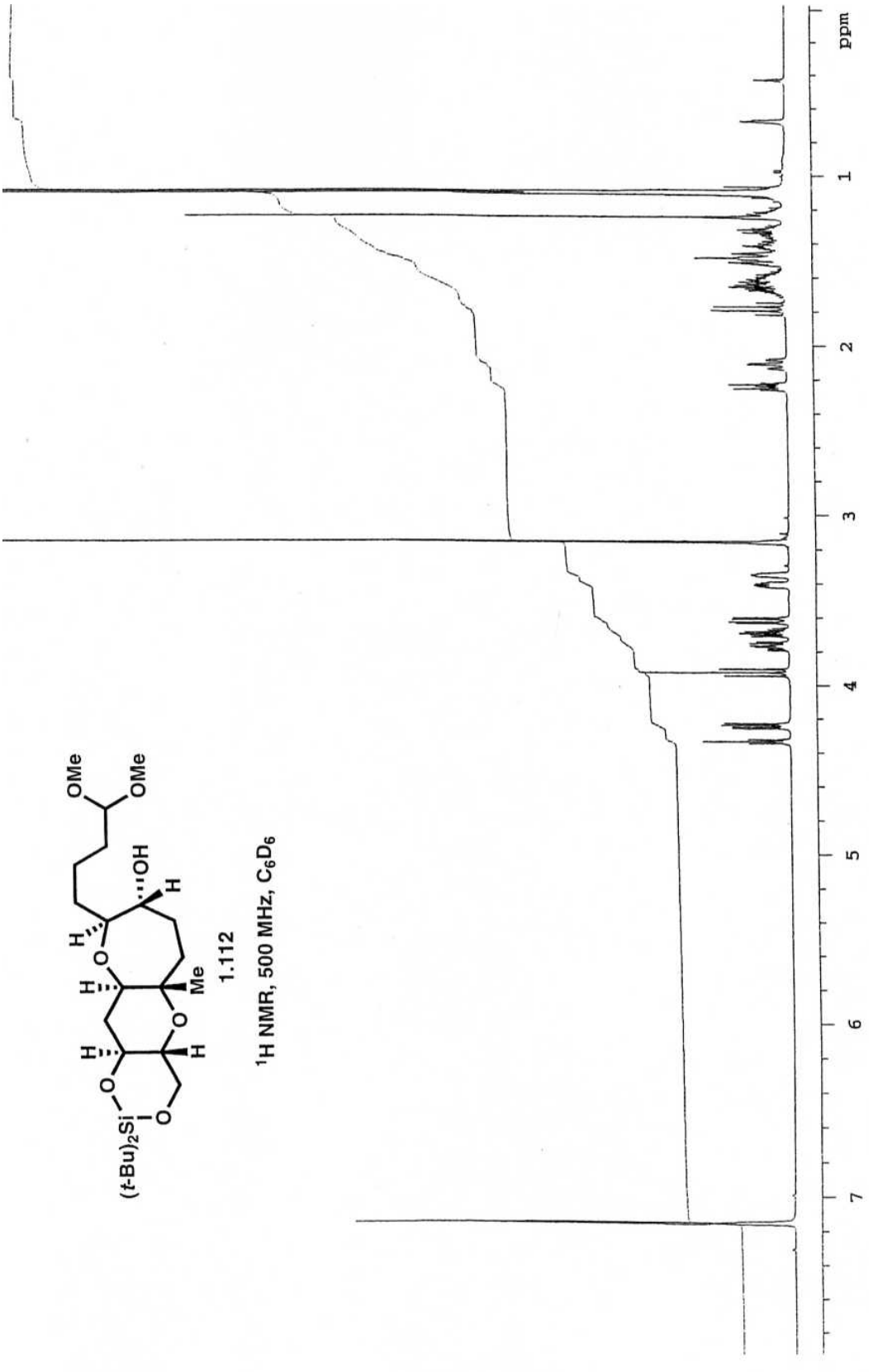
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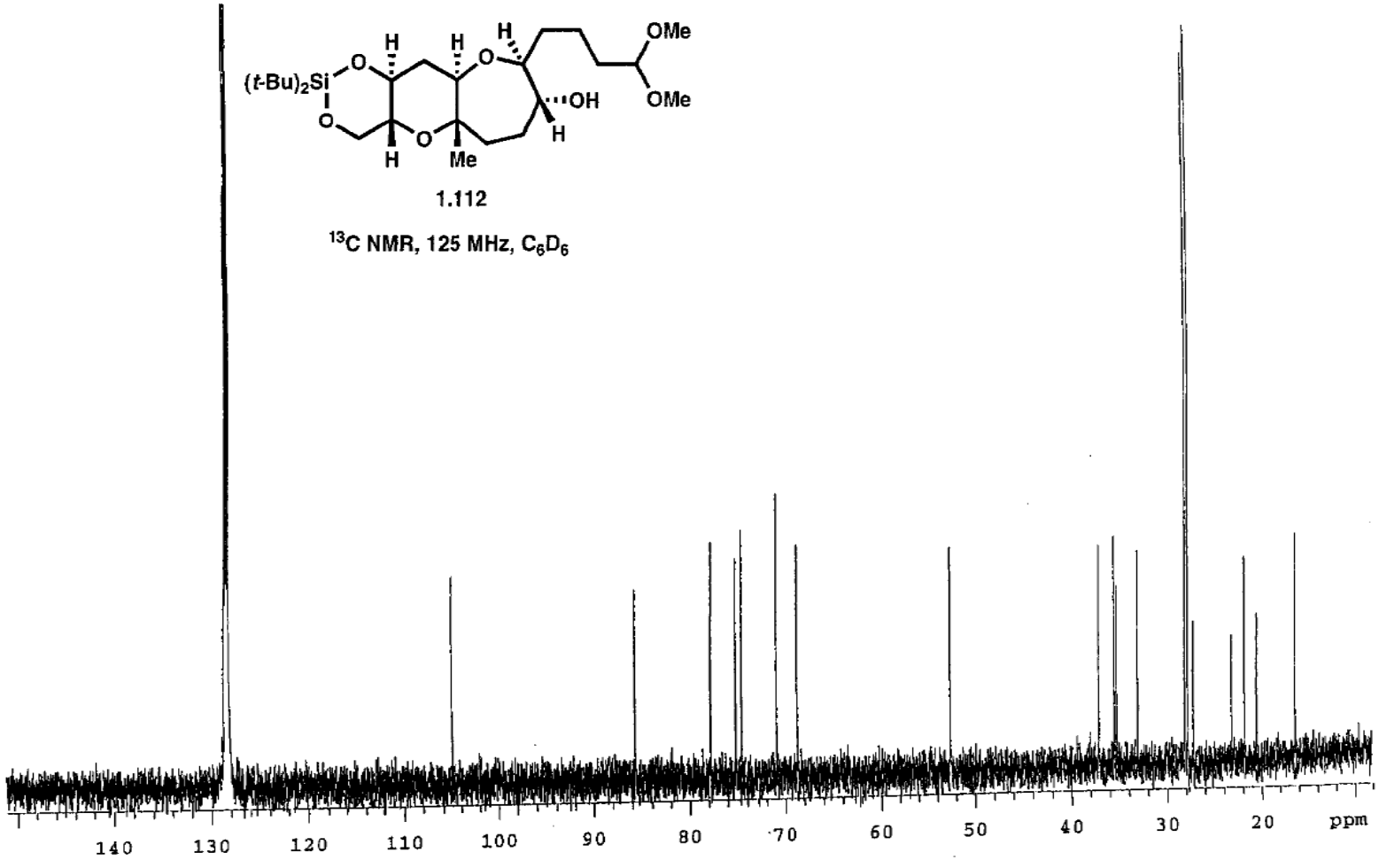

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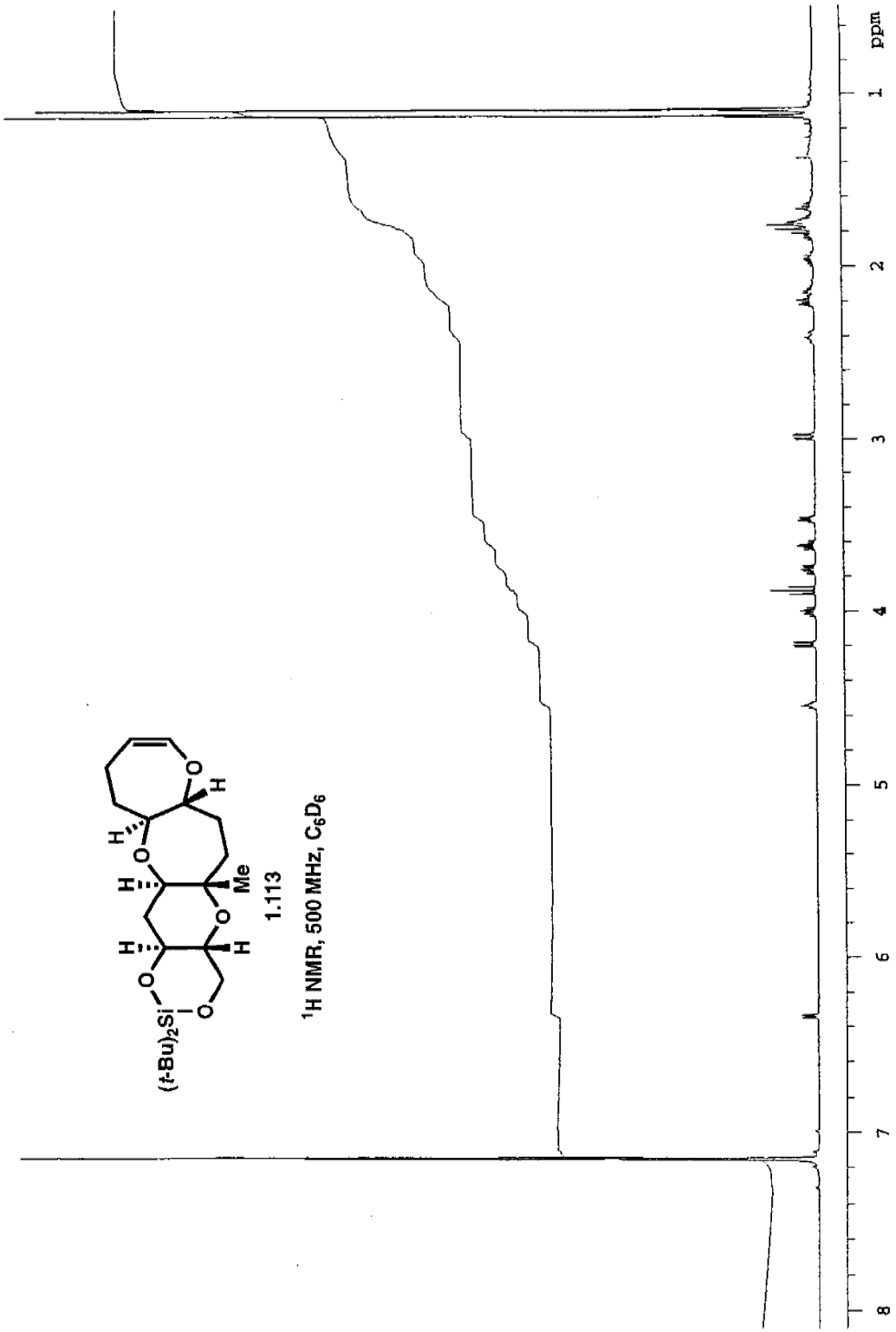
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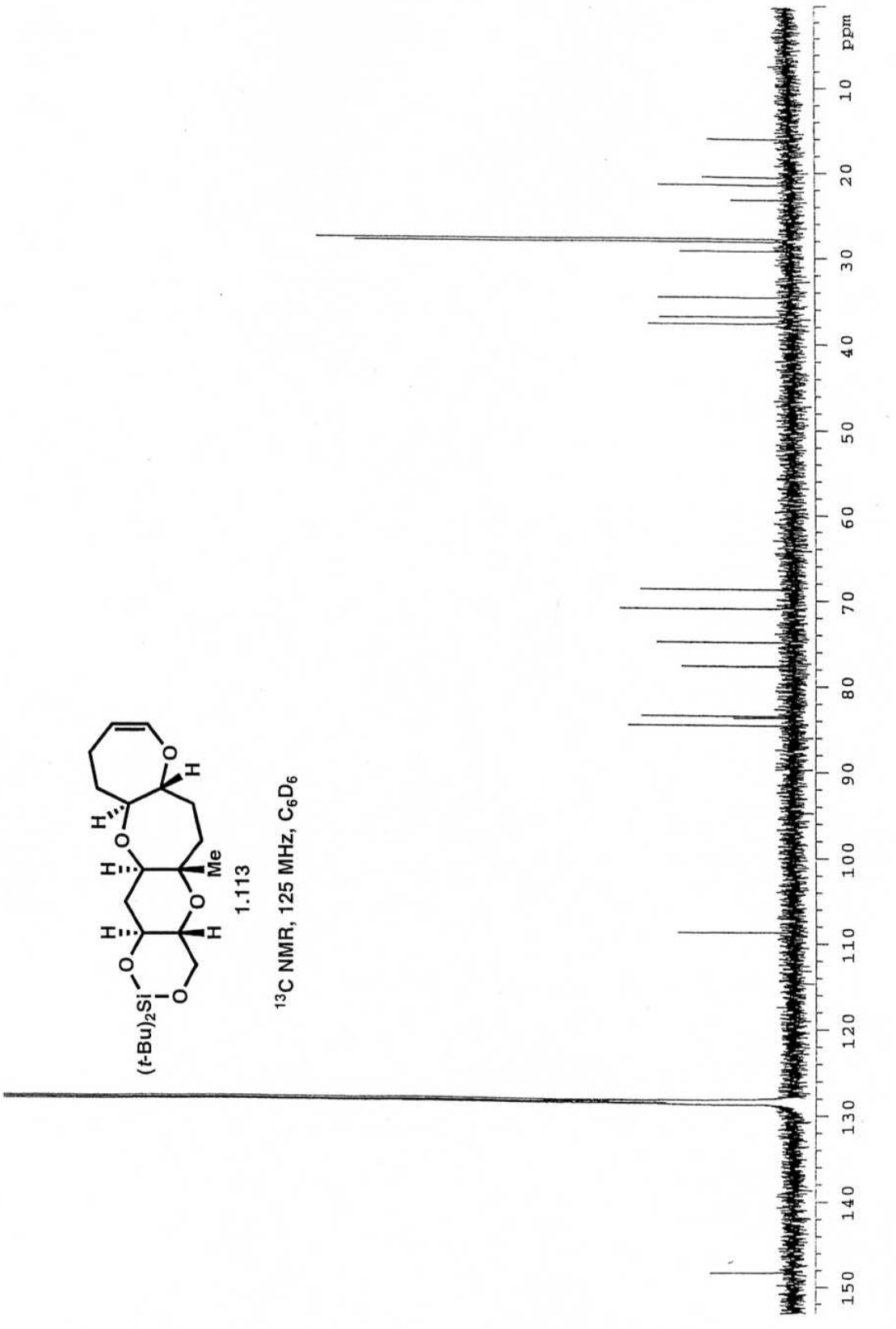
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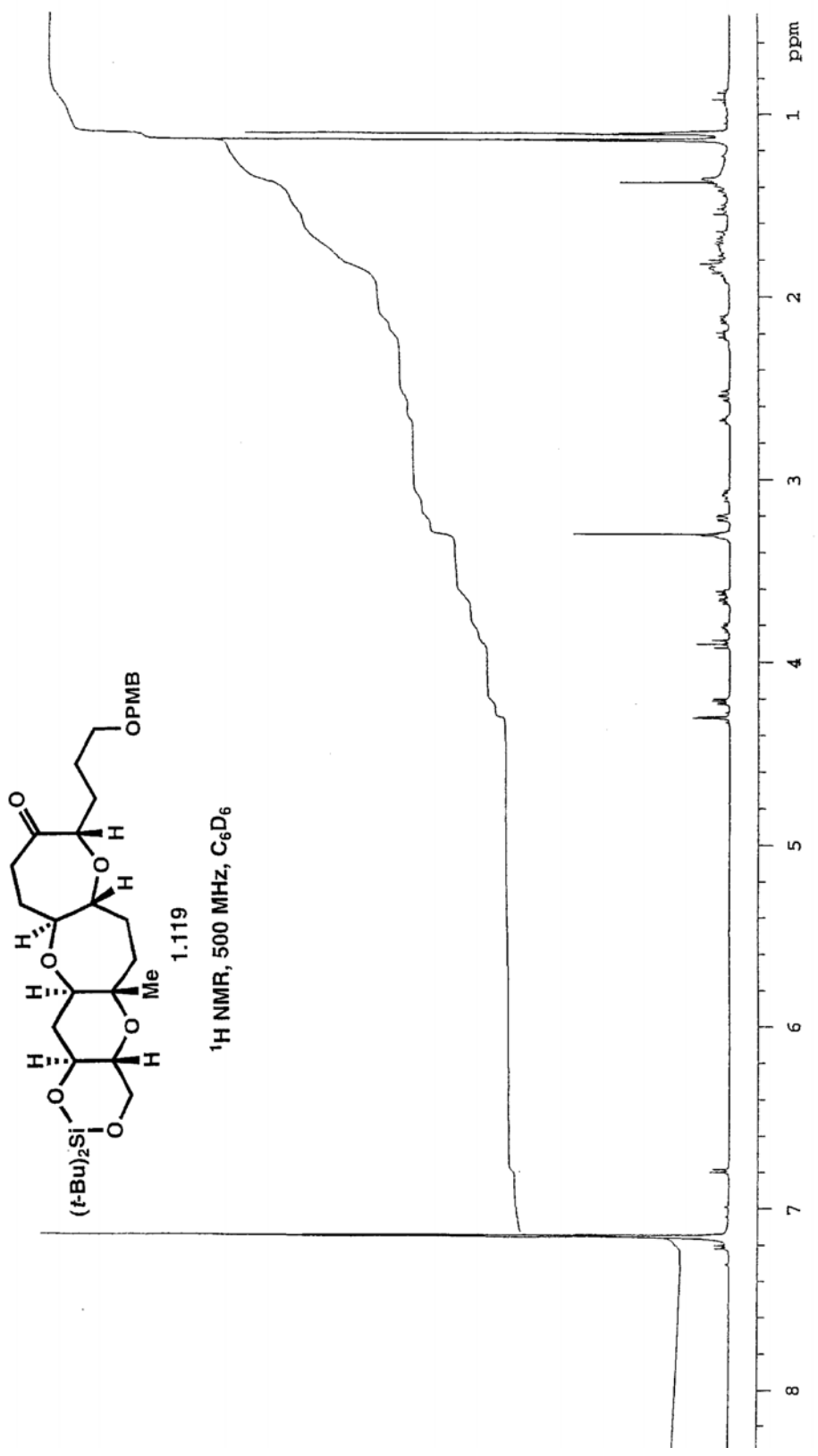
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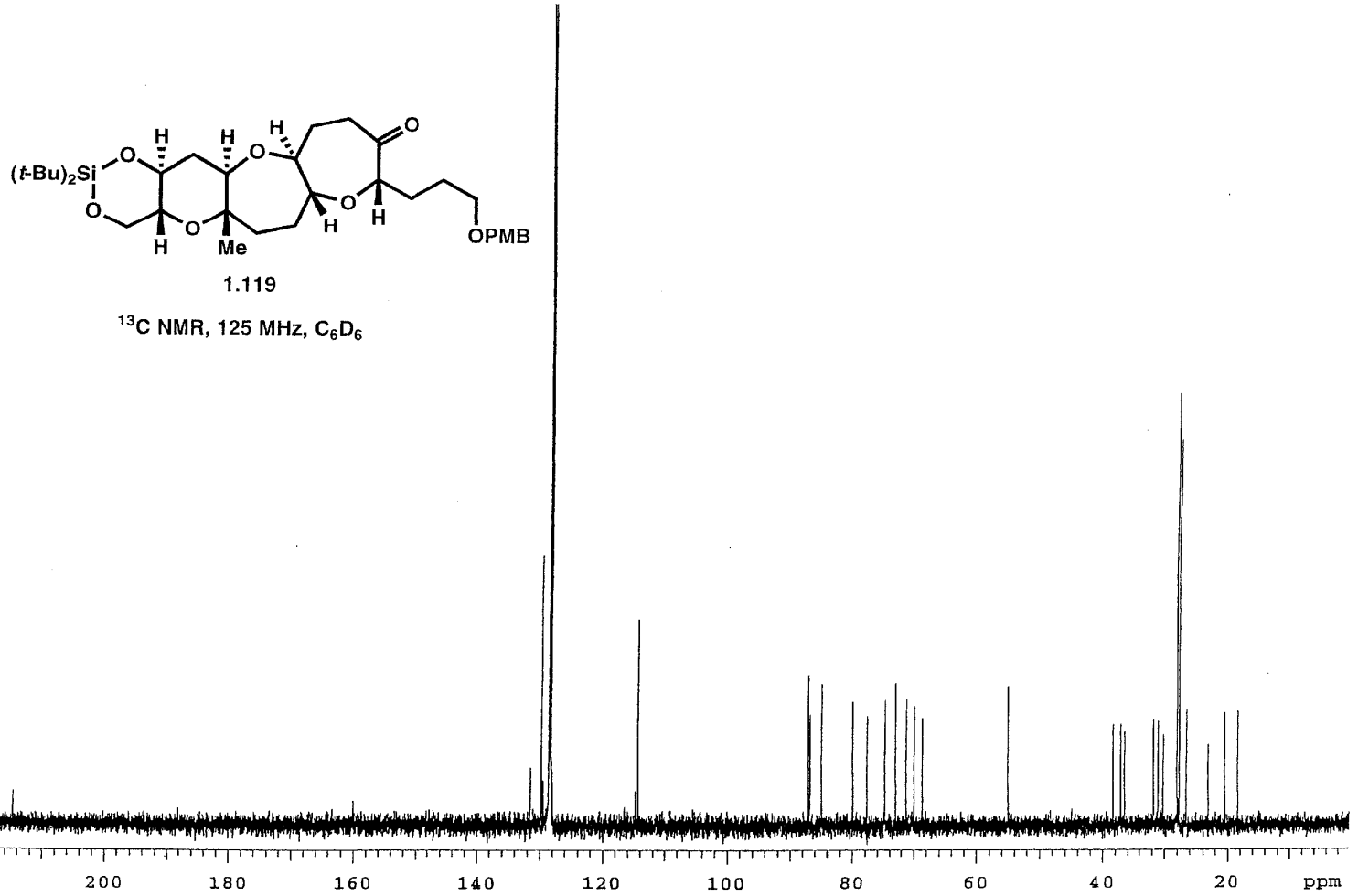

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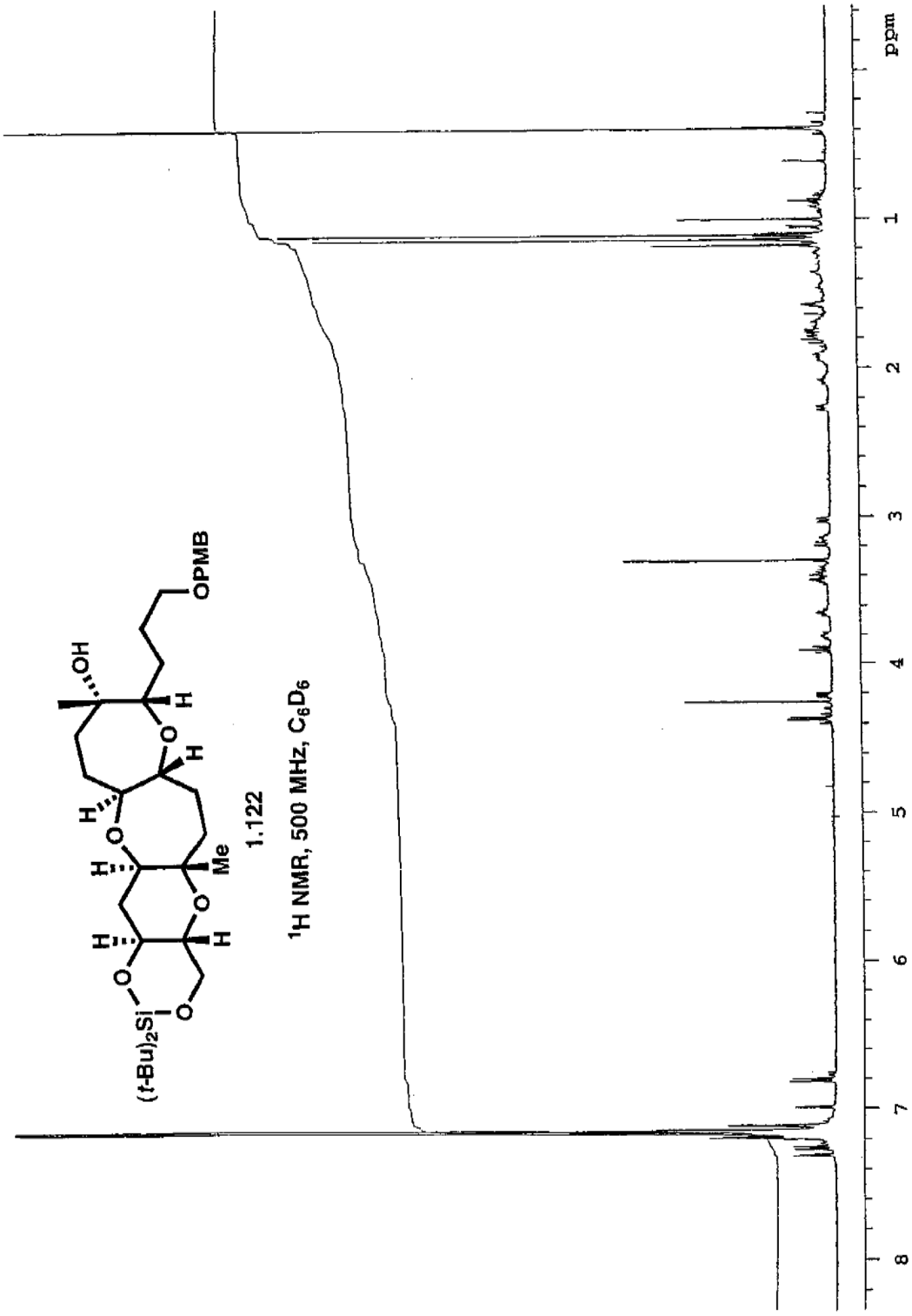
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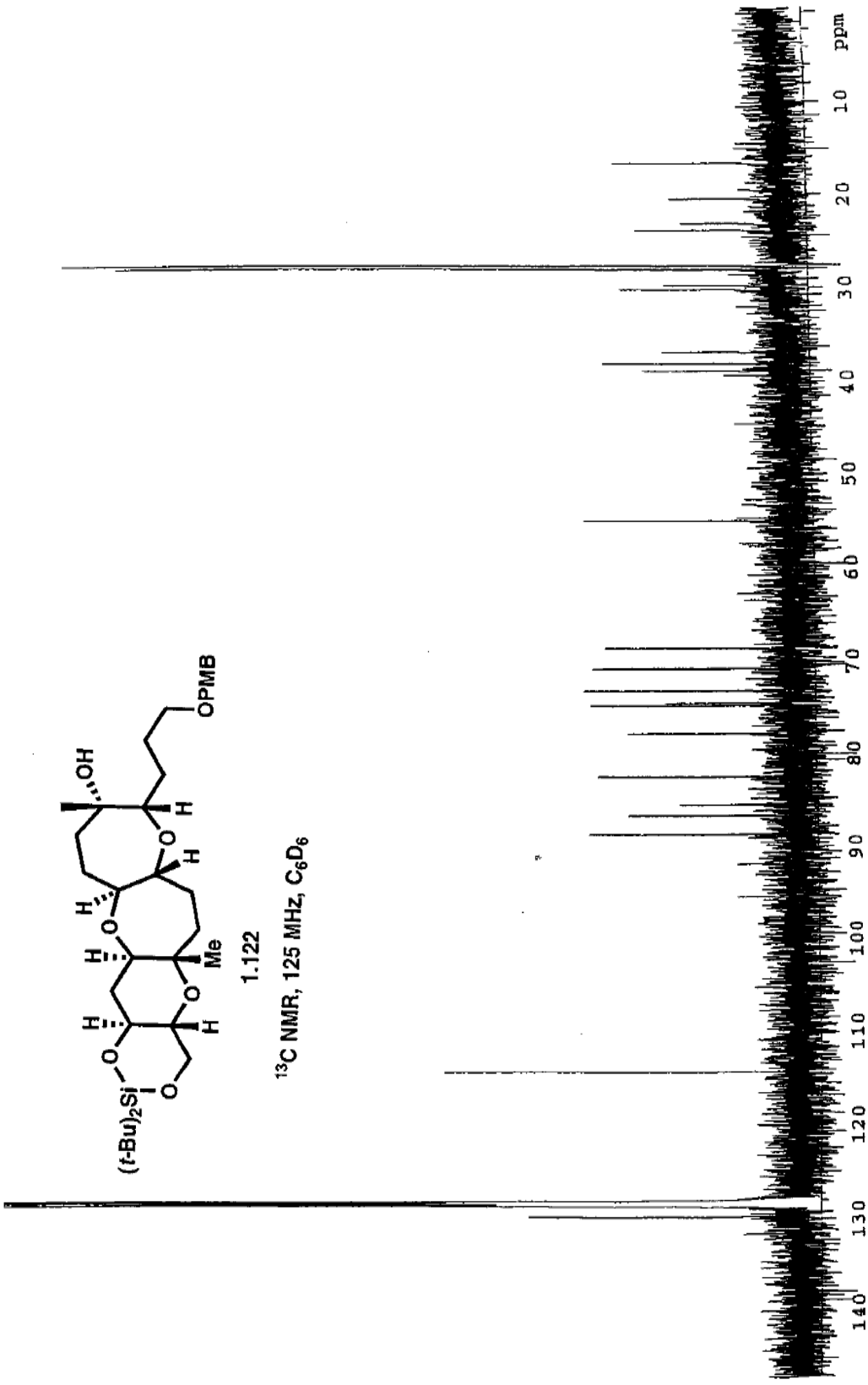
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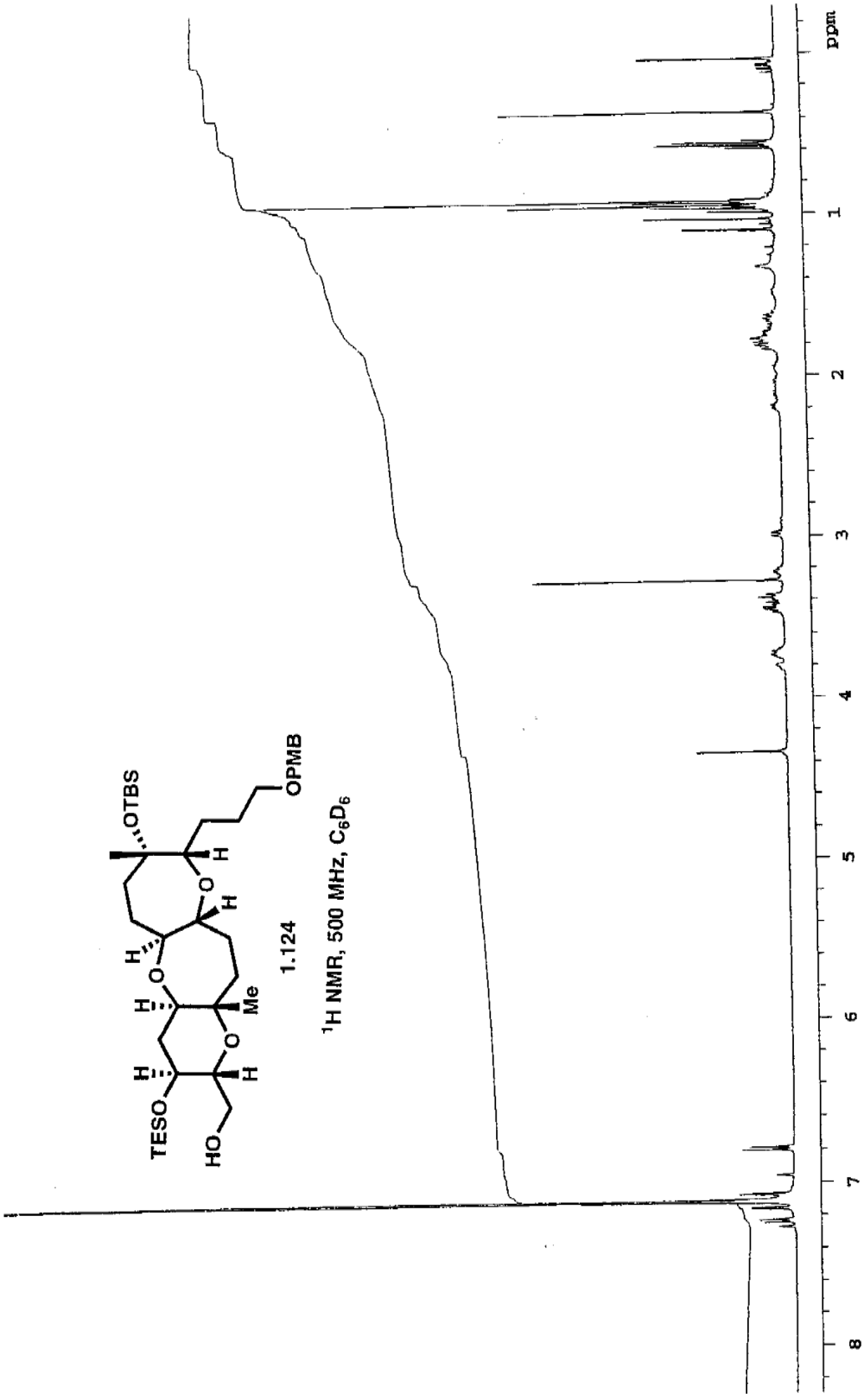
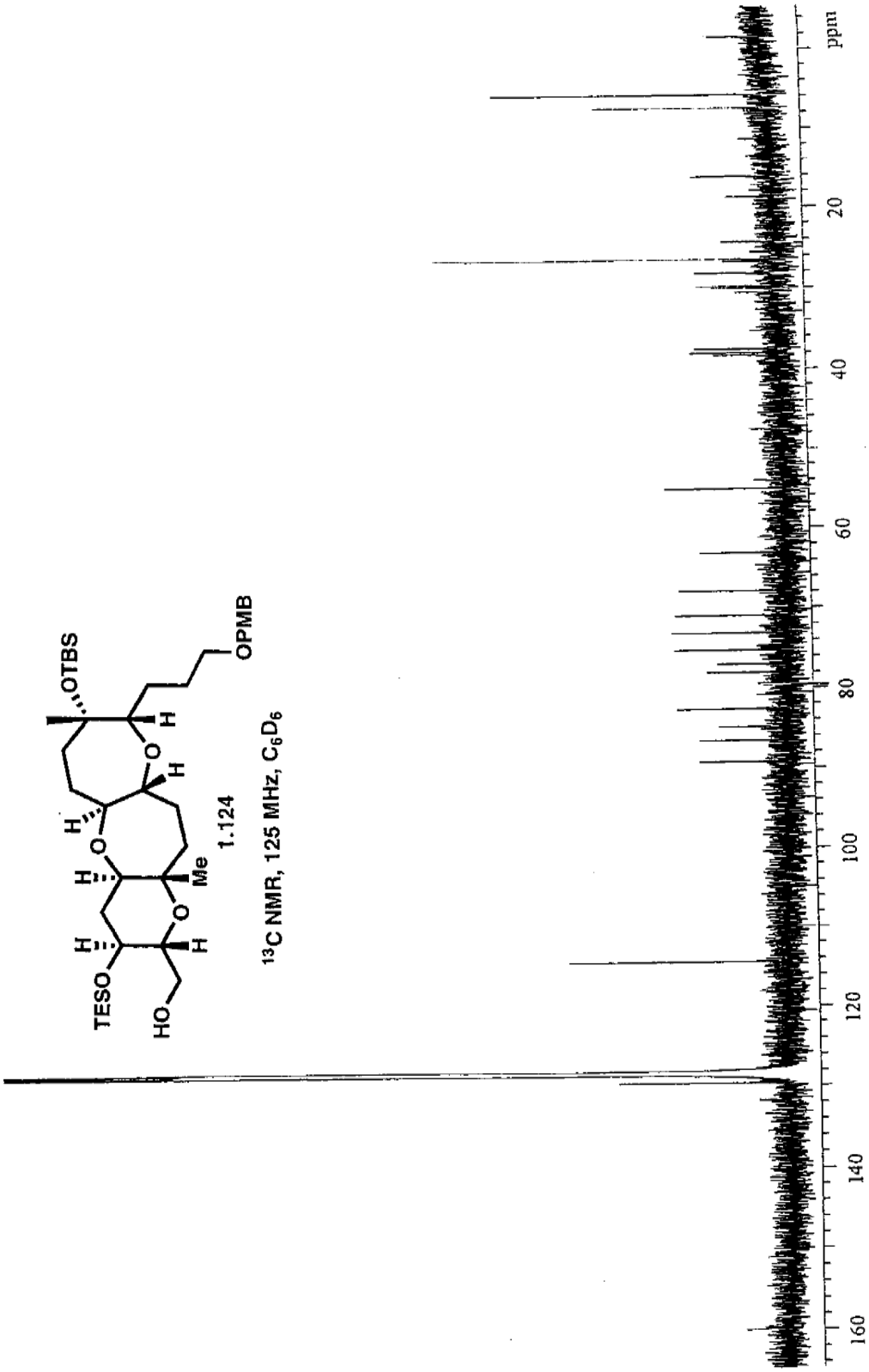
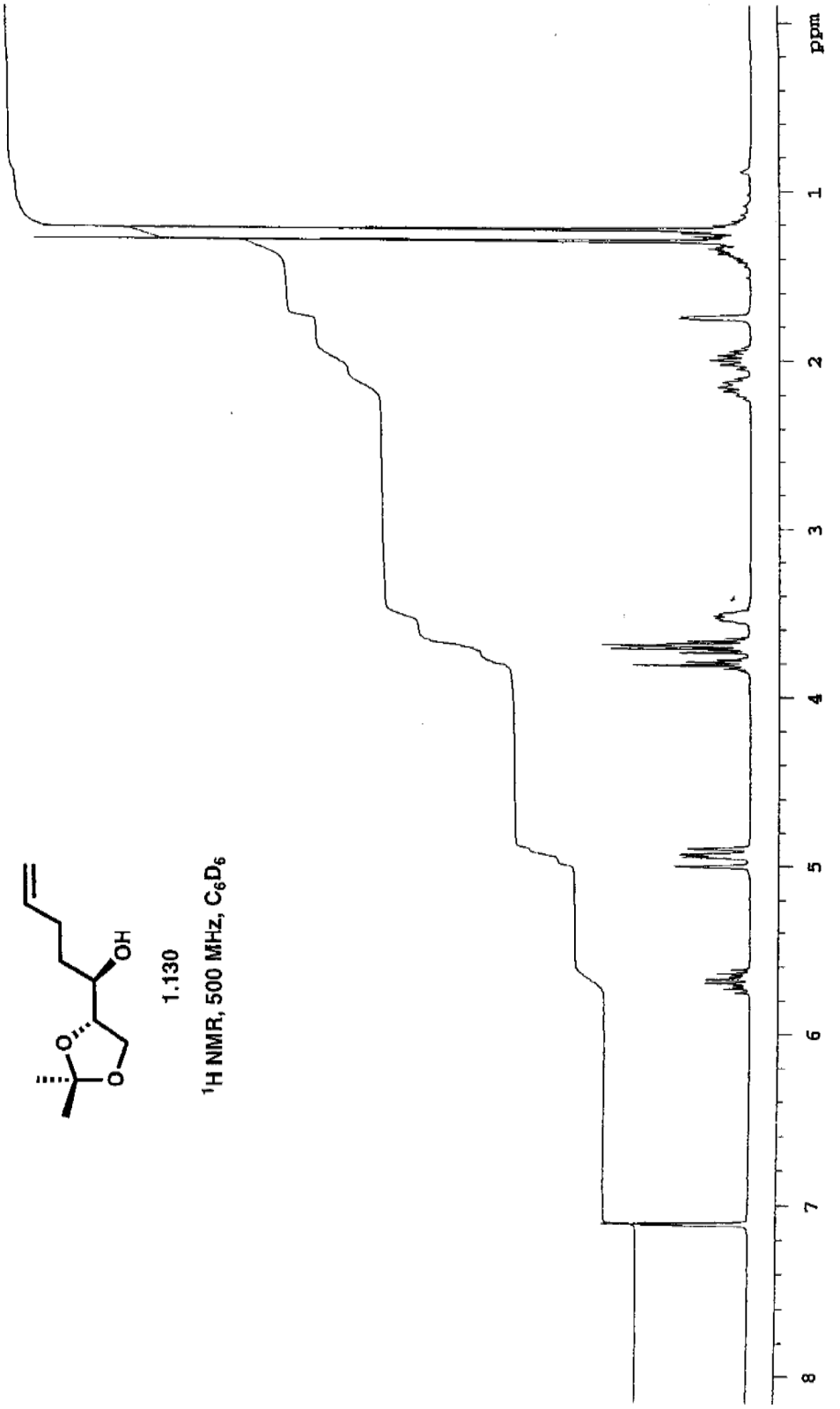
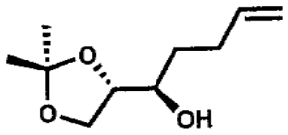
90
100
110
120
130
140


OTBS
OPMB
TESO
HO
Me
1.124
^{1}H NMR, 500 MHz, C_6D_6
ppm
1
2
3
4
5
6
7
8

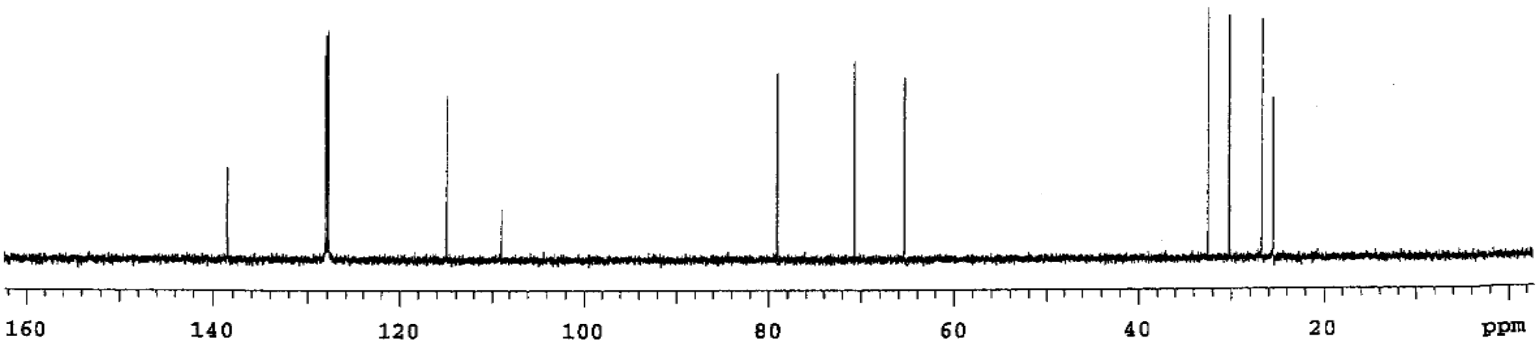

OTBS
OPMB
TESO
HO
Me
1.124
^{13}C NMR, 125 MHz, C_6D_6
ppm
160
140
120
100
80
60
40
20

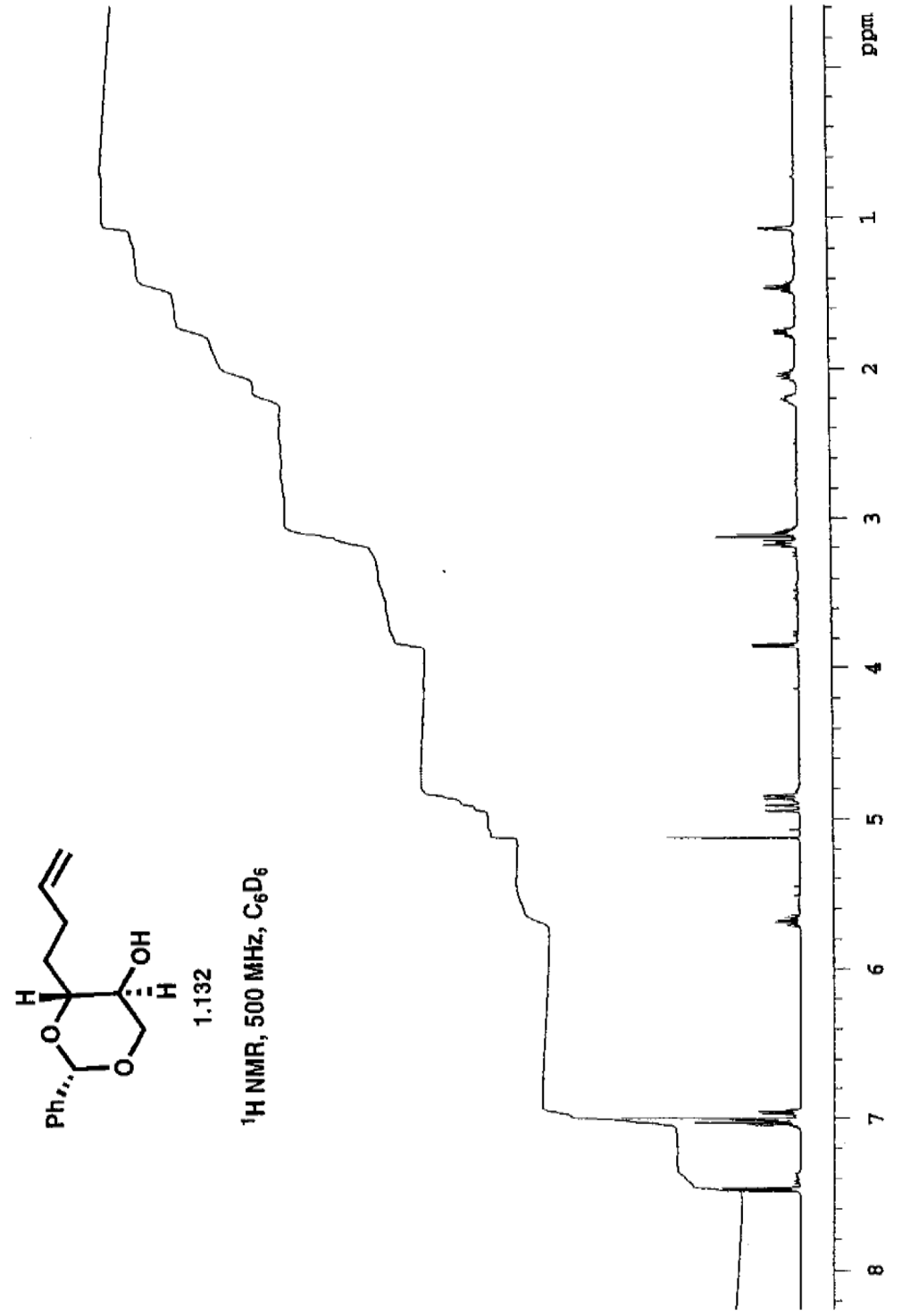

OH
1.130
^{1}H NMR, 500 MHz, C_6D_6
ppm
1
2
3
4
5
6
7
8

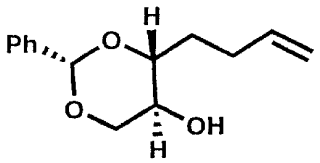


1.130

^{13}C NMR, 125 MHz, C_6D_6

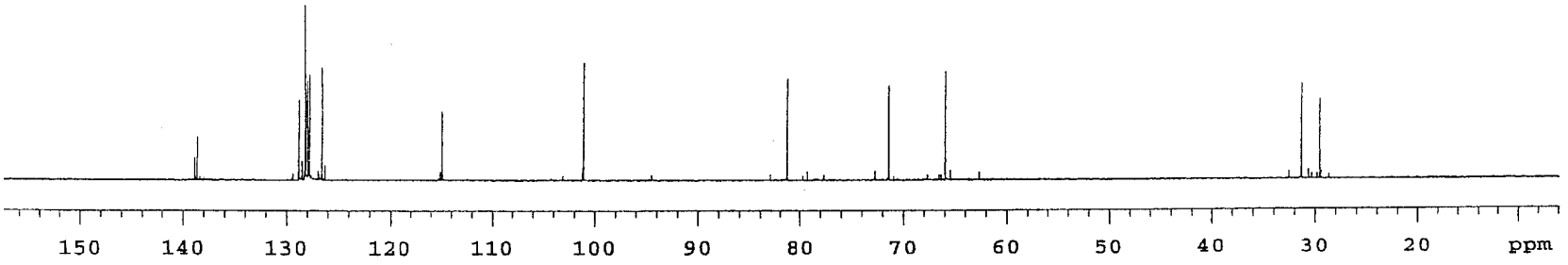


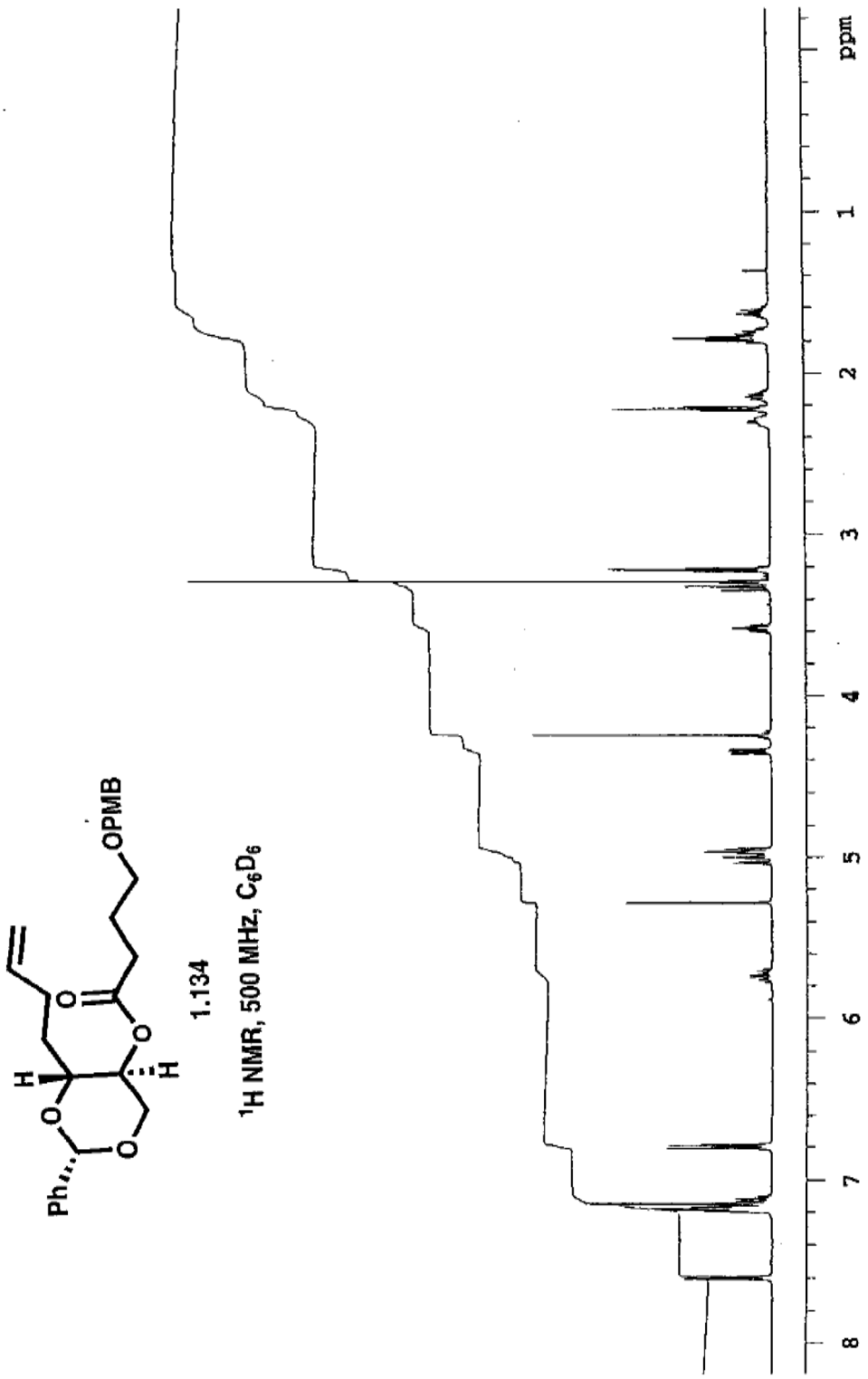

H
O
OH
H
O
Ph
1.132
^{1}H NMR, 500 MHz, C_6D_6
ppm
1
2
3
4
5
6
7
8

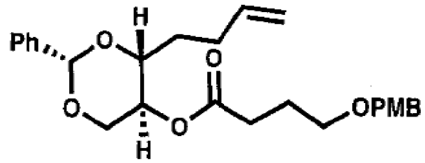


1.132

^{13}C NMR, 125 MHz, C_6D_6

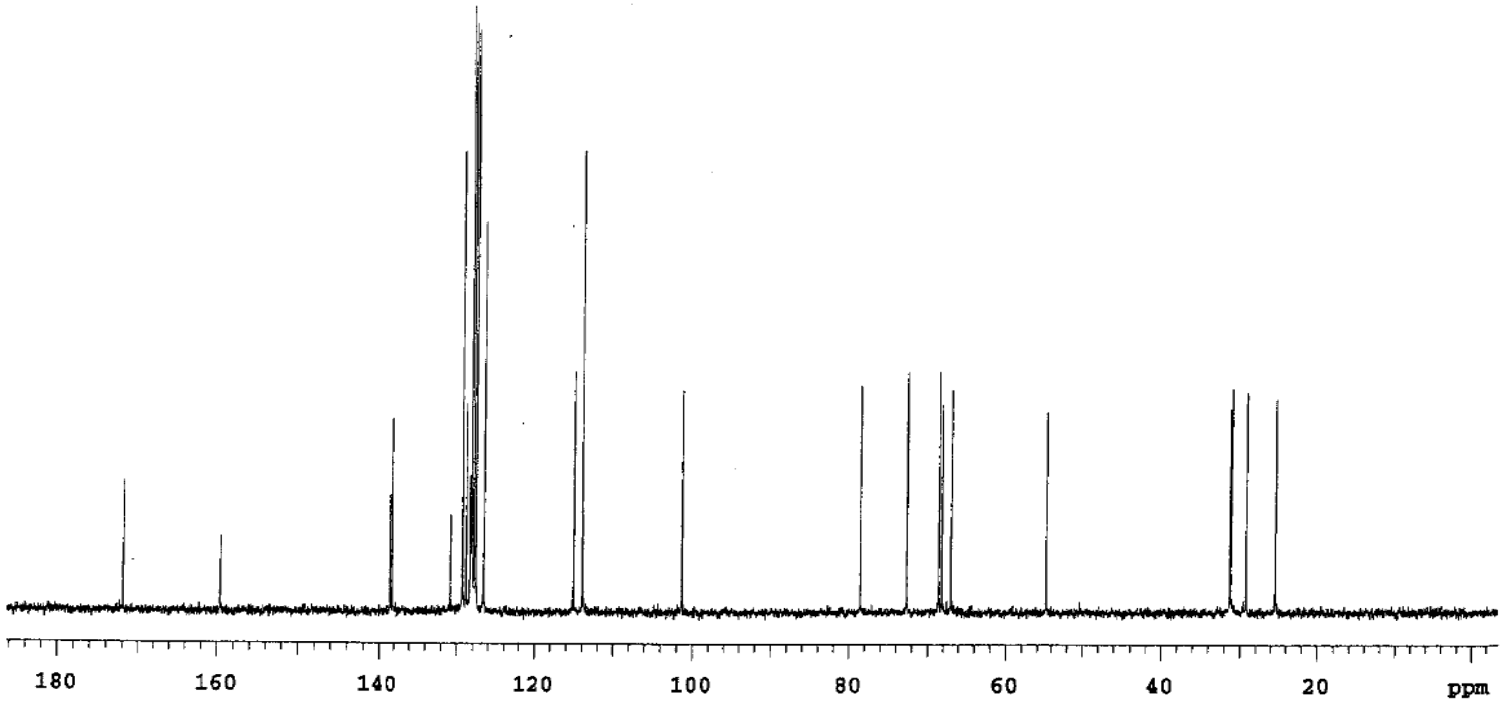


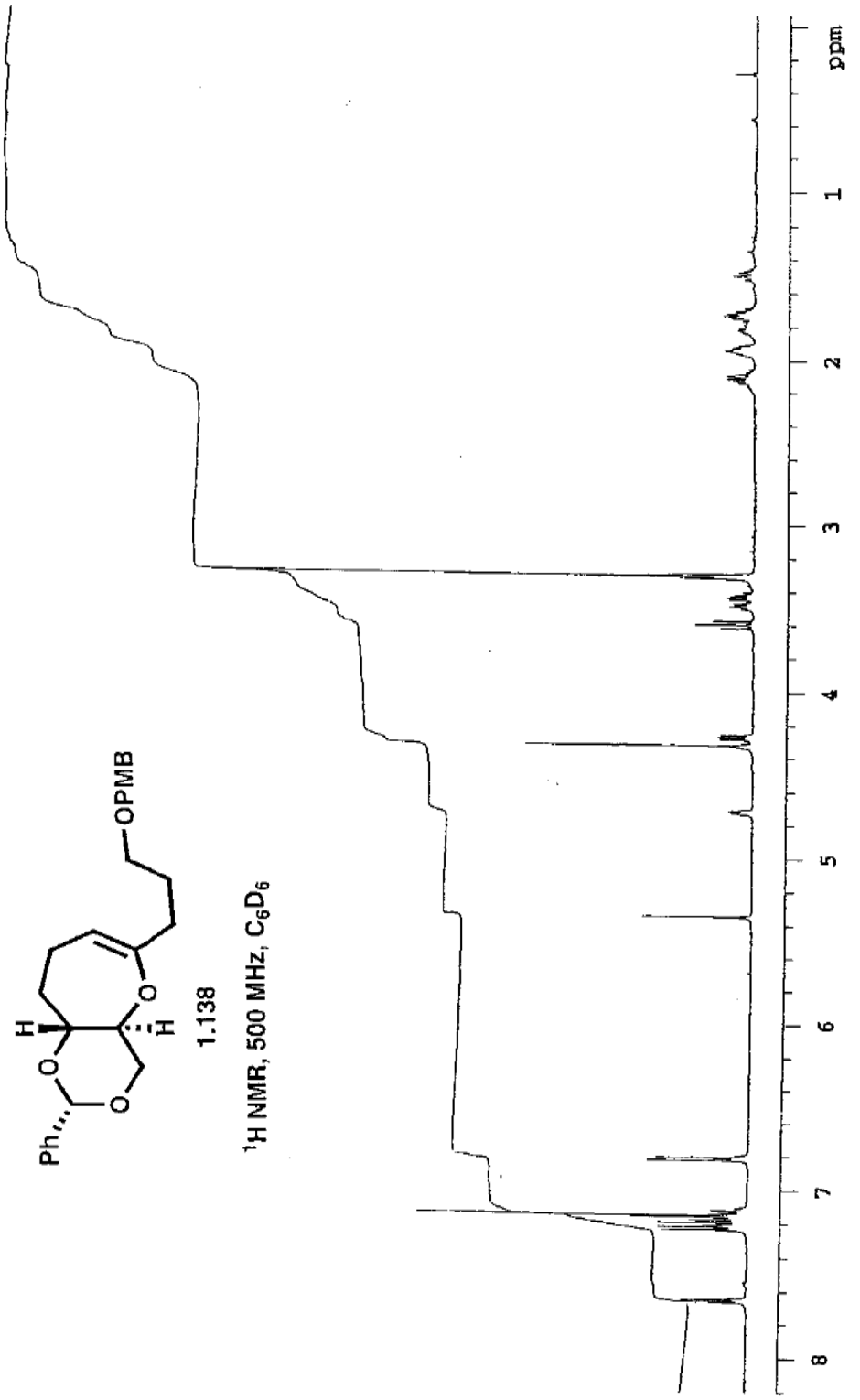

OPMB
O
O
H
O
O
H
O
Ph
1.134
^{1}H NMR, 500 MHz, C_6D_6
ppm
1
2
3
4
5
6
7
8

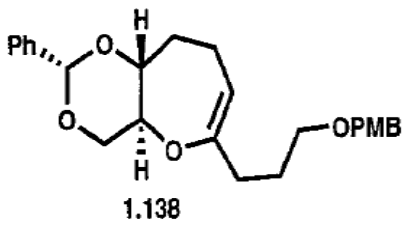


1.134

^{13}C NMR, 125 MHz, C_6D_6

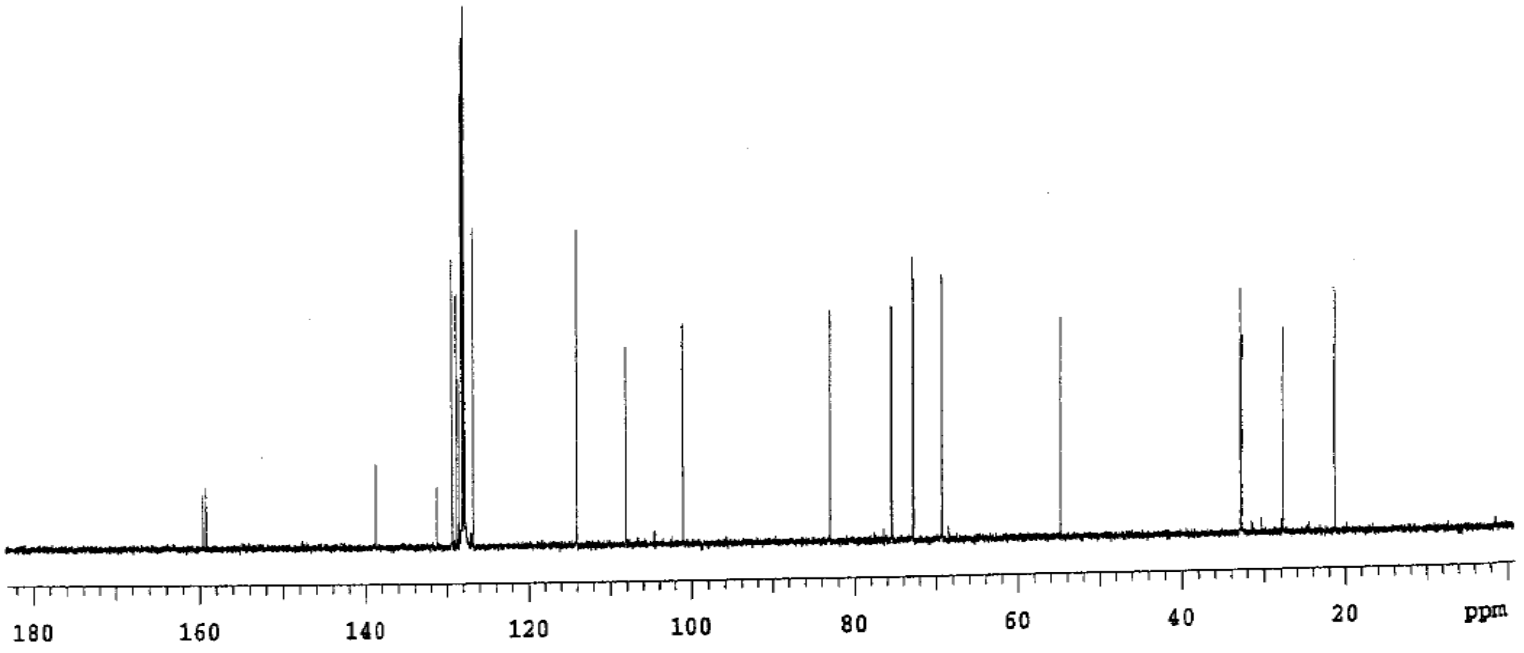


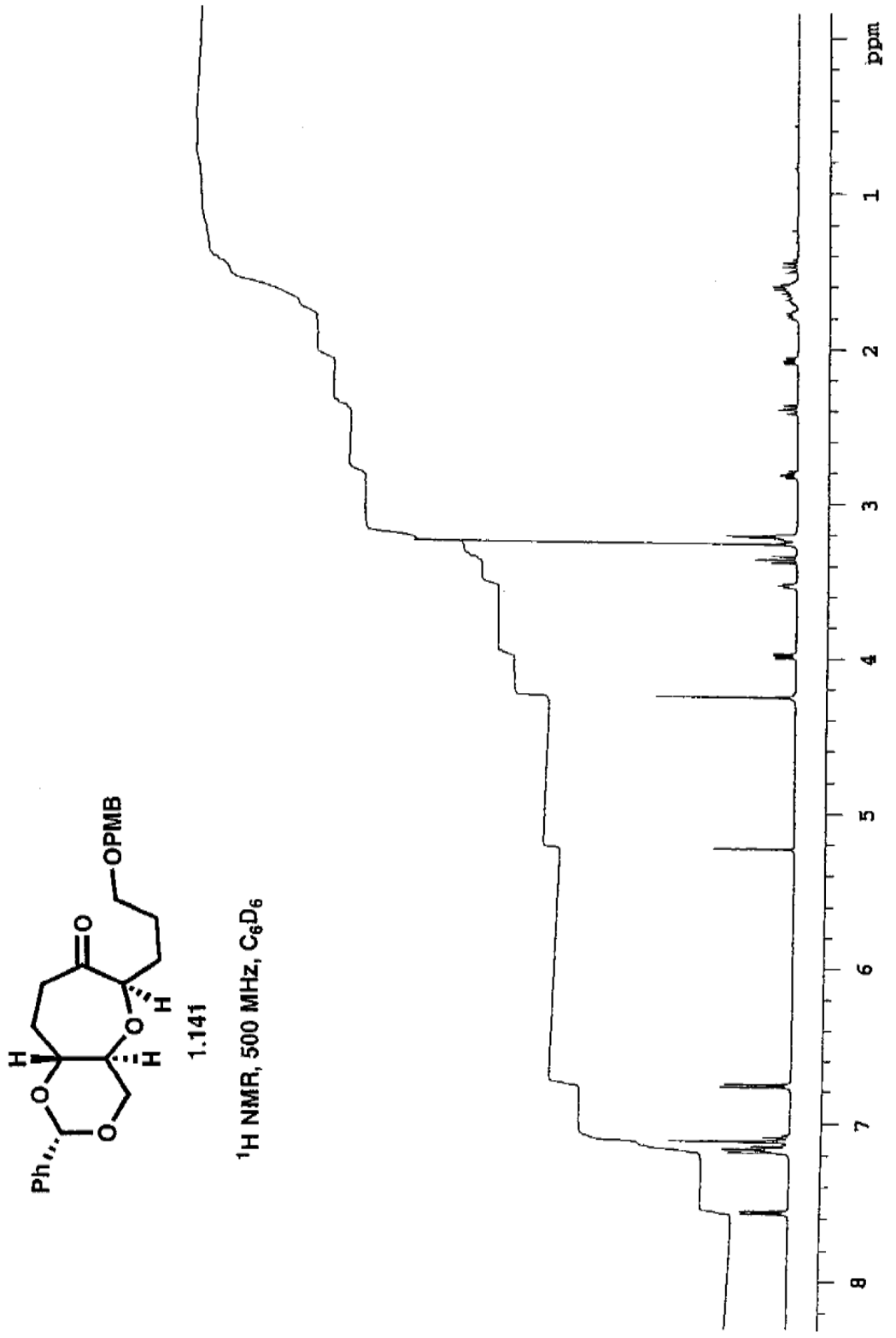

OPMB
H
O
O
H
O
O
Ph
1.138
^{1}H NMR, 500 MHz, C_6D_6
ppm
1
2
3
4
5
6
7
8

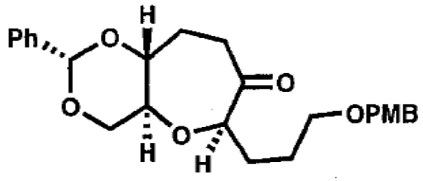


1.138

^{13}C NMR, 125 MHz, C_6D_6

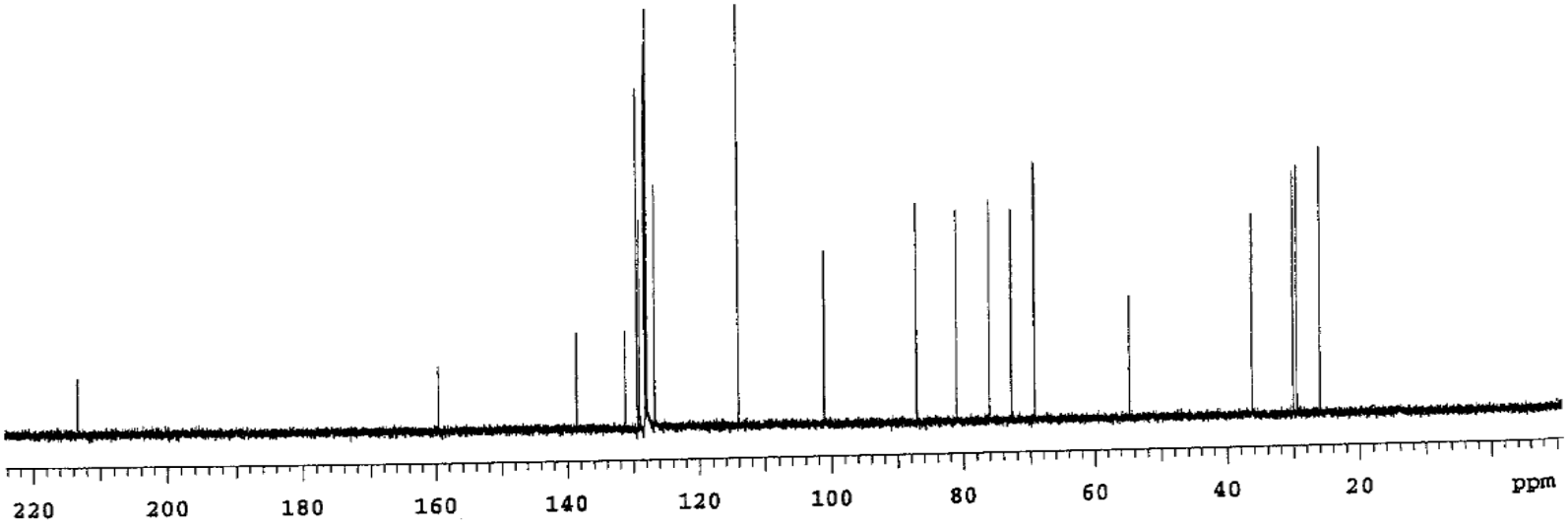


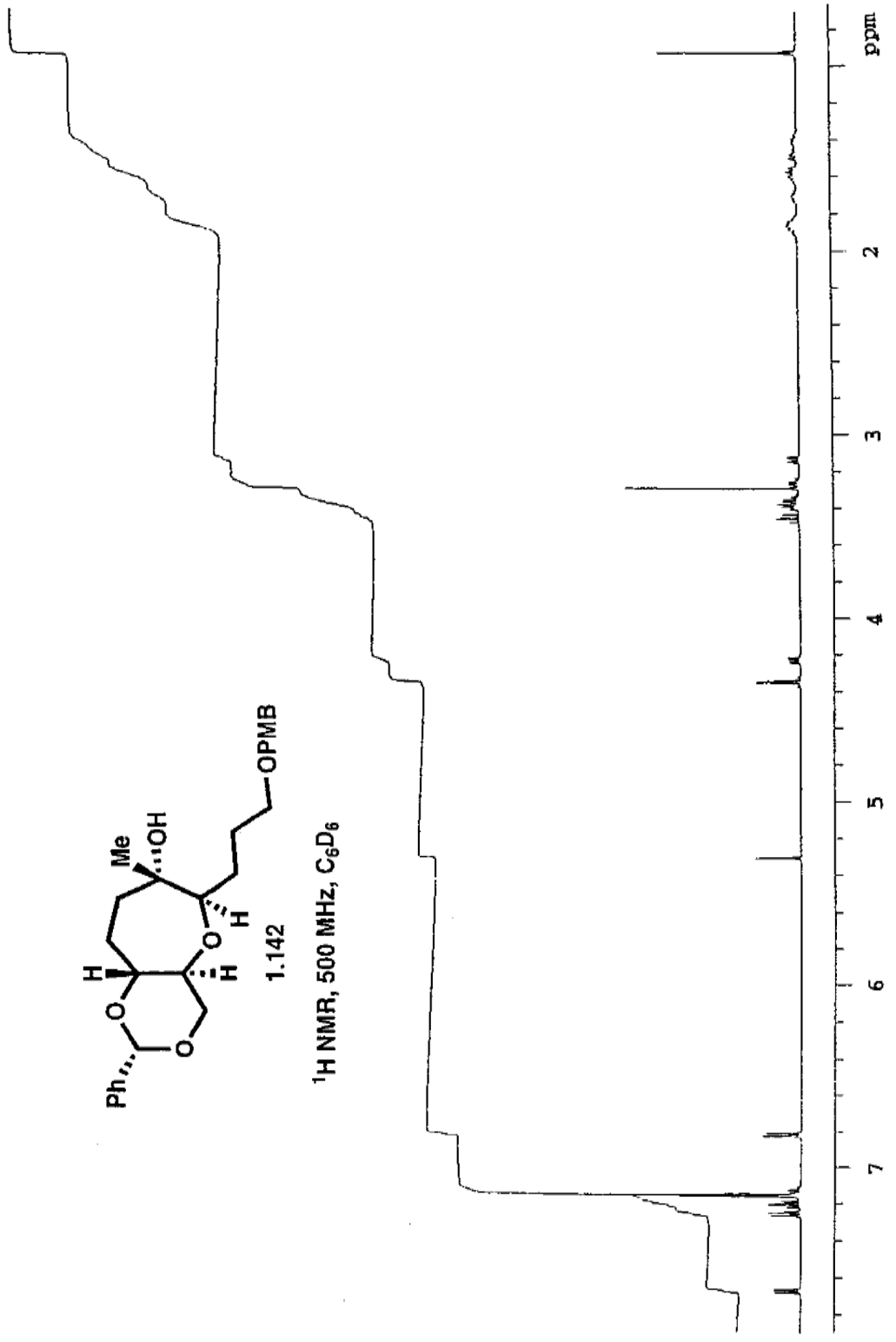

OPMB
O
H
O
H
O
Ph
O
1.141
^{1}H NMR, 500 MHz, C_6D_6
8
7
6
5
4
3
2
1
ppm

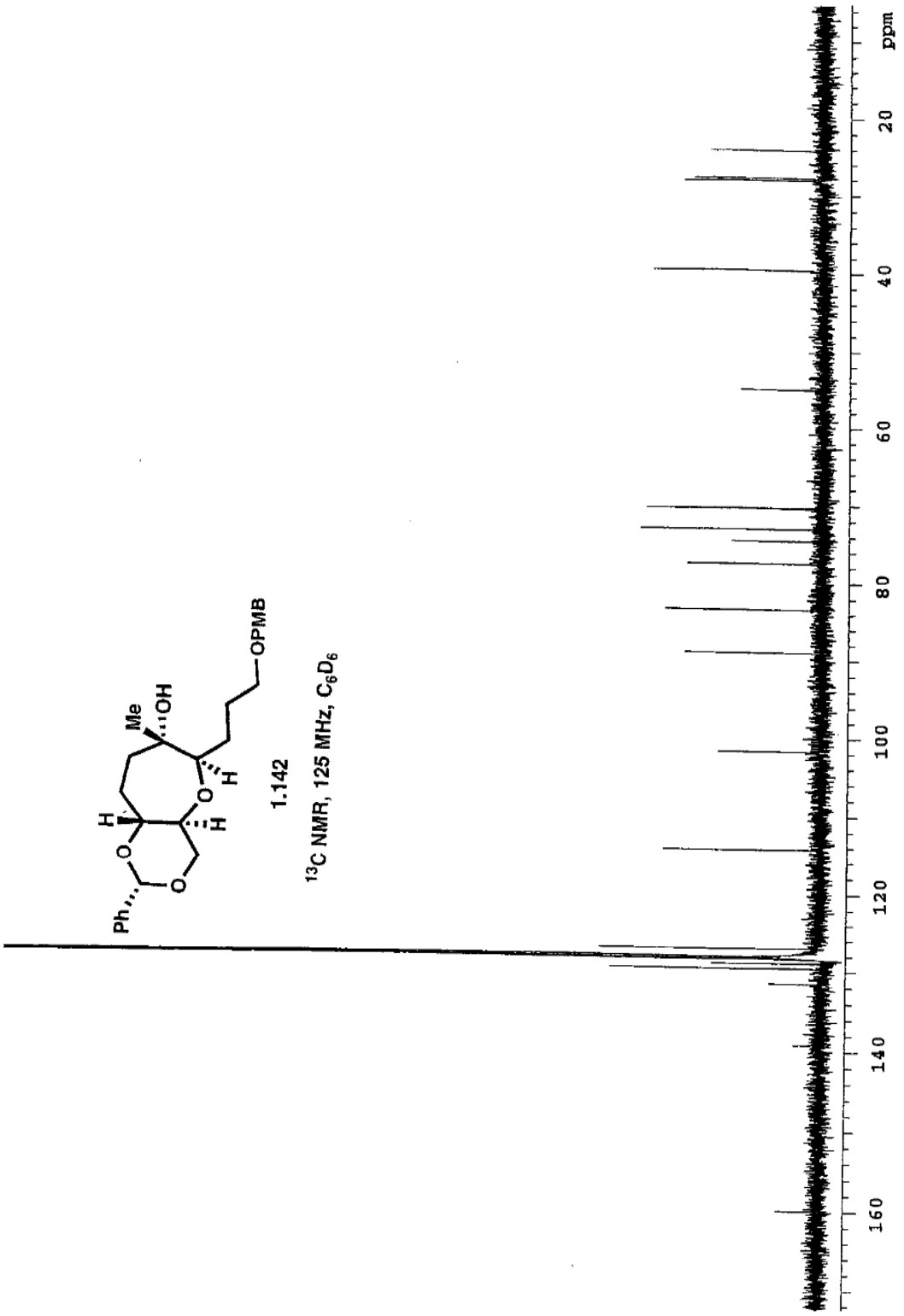


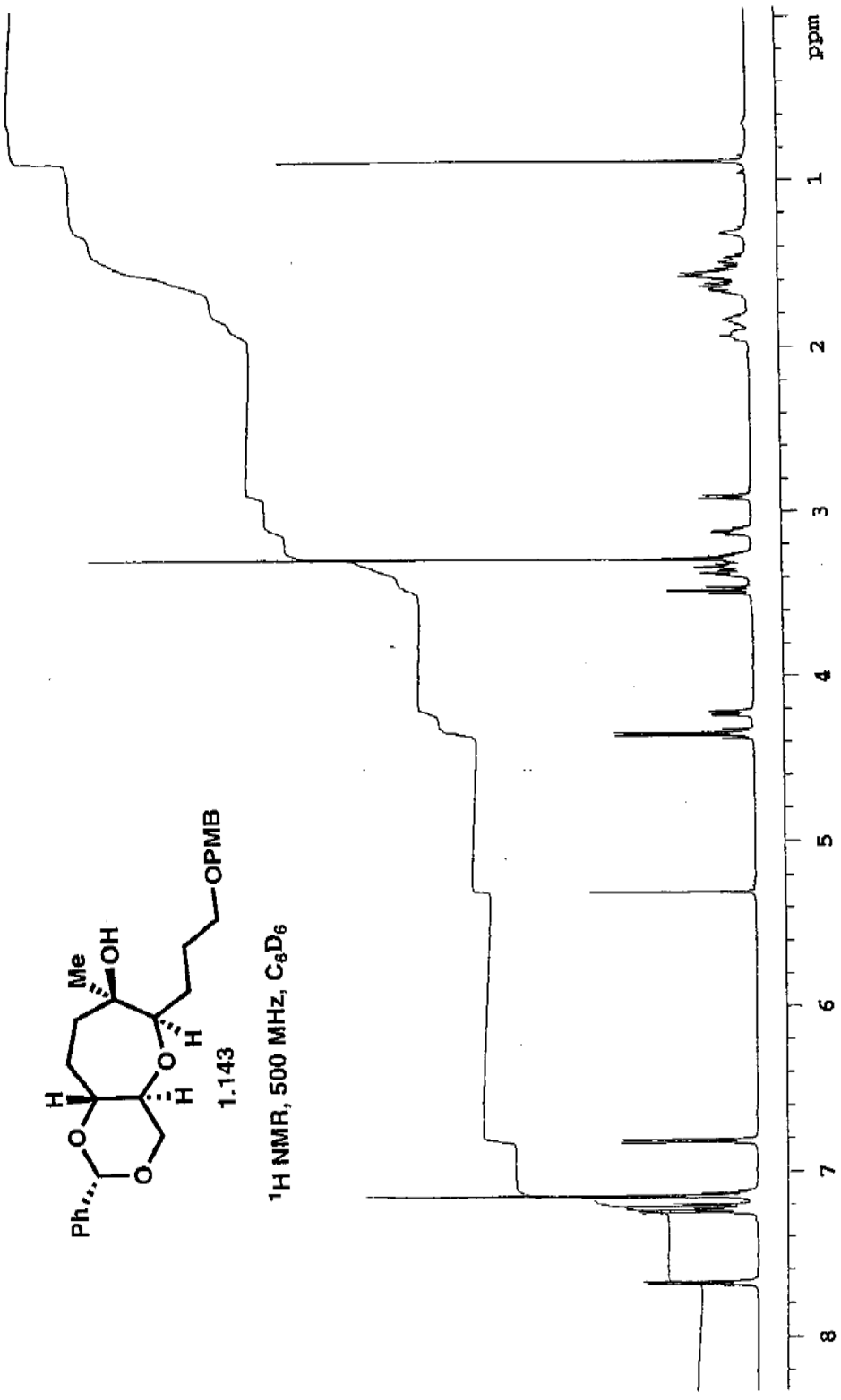
1.141

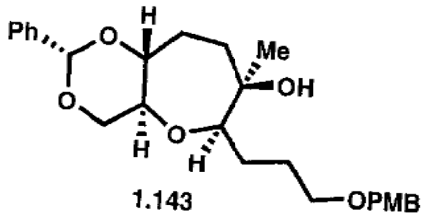
^{13}C NMR, 125 MHz, C_6D_6




Me
OH
H
O
H
OPMB
O
O
Ph
1.142
^{1}H NMR, 500 MHz, C_6D_6
7
6
5
4
3
2
ppm

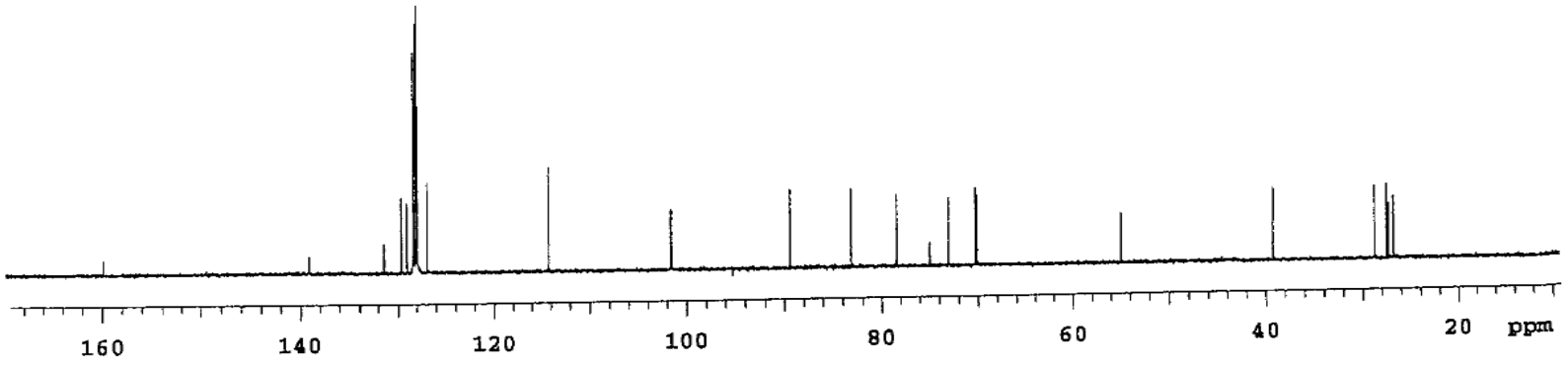

Ph
O
O
H
O
H
H
Me
OH
OPMB
1.142
^{13}C NMR, 125 MHz, C_6D_6
160
140
120
100
80
60
40
20
ppm

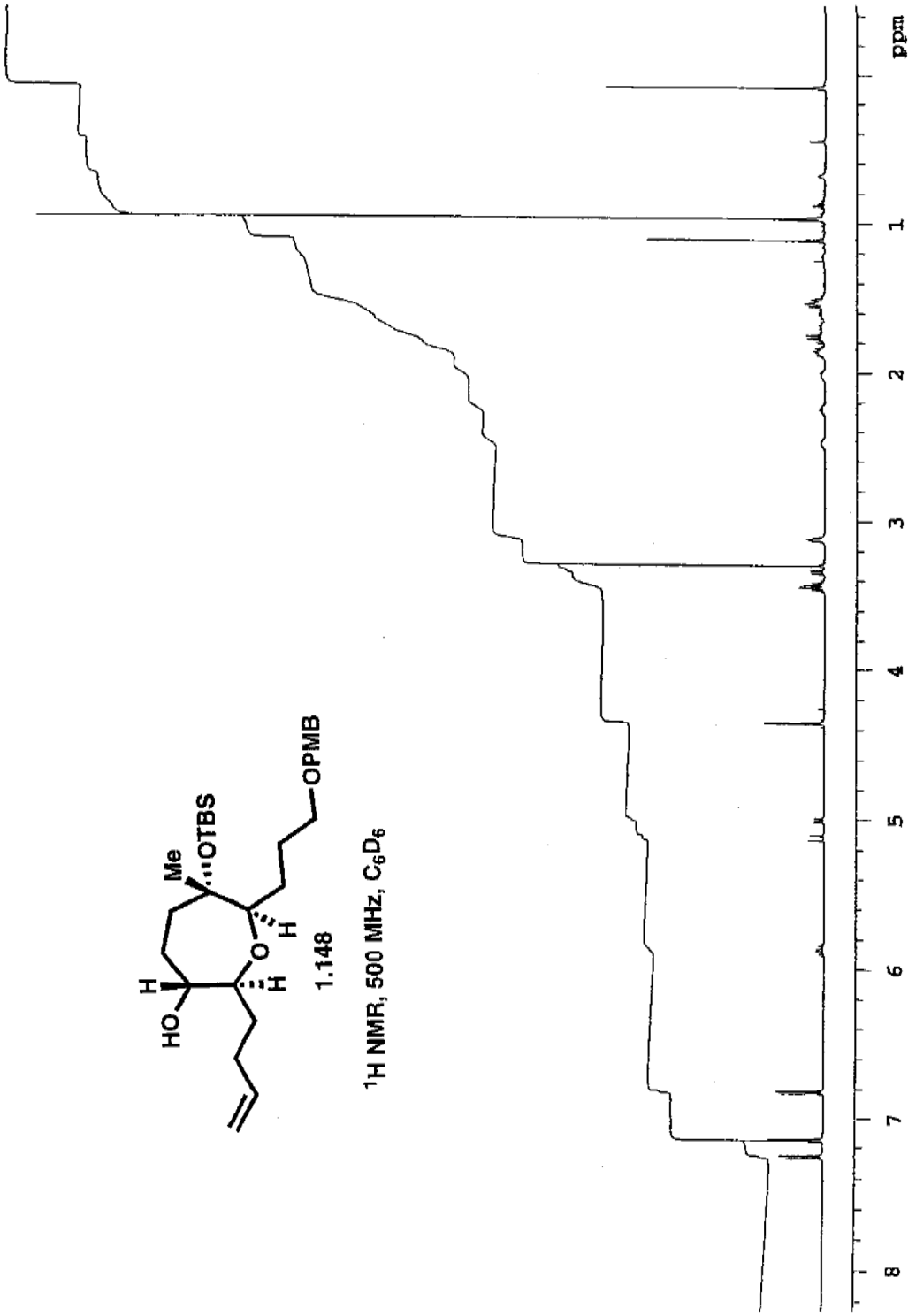

Me
OH
OPMB
H
O
H
H
O
O
Ph
1.143
^{1}H NMR, 500 MHz, C_6D_6
ppm
1
2
3
4
5
6
7
8

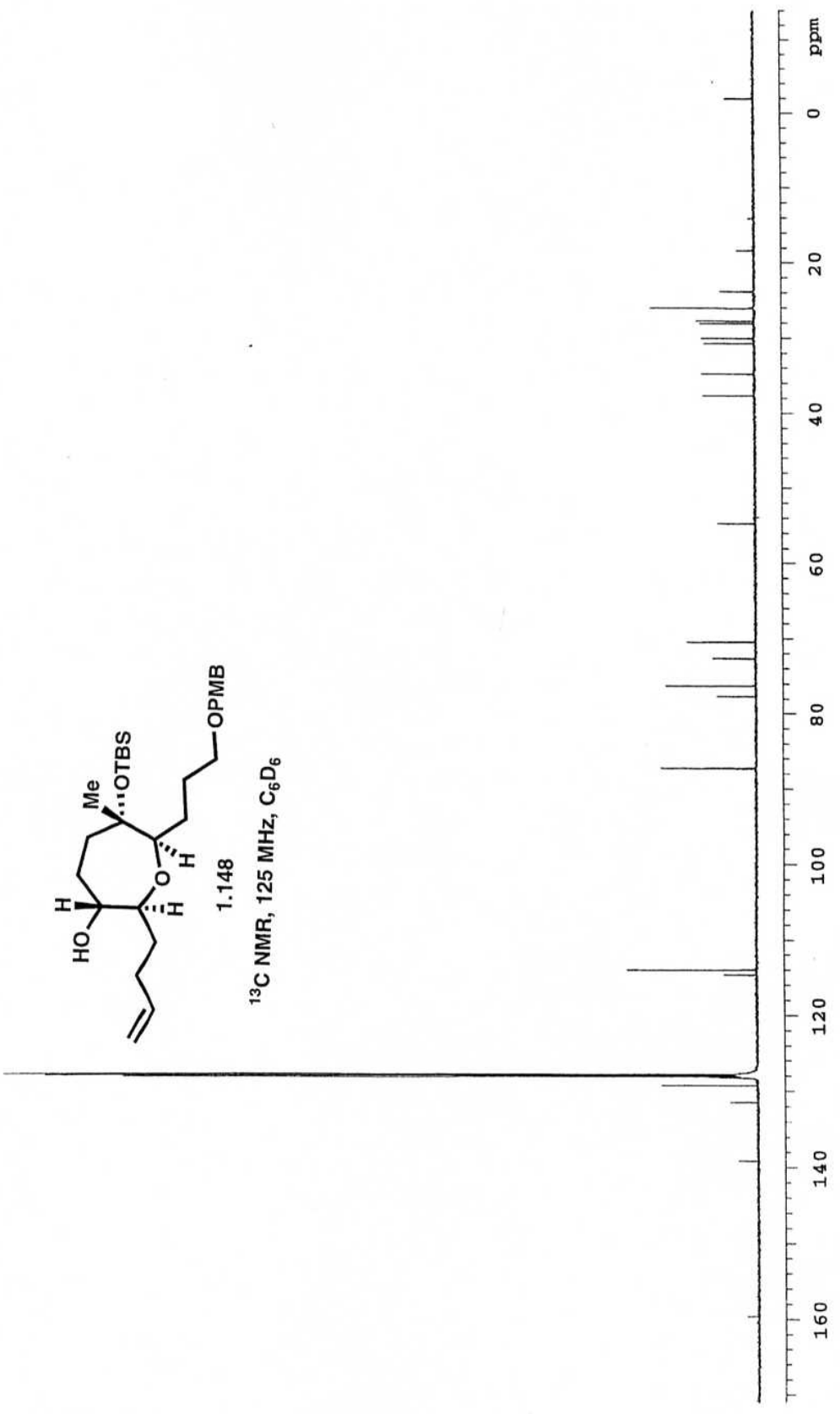


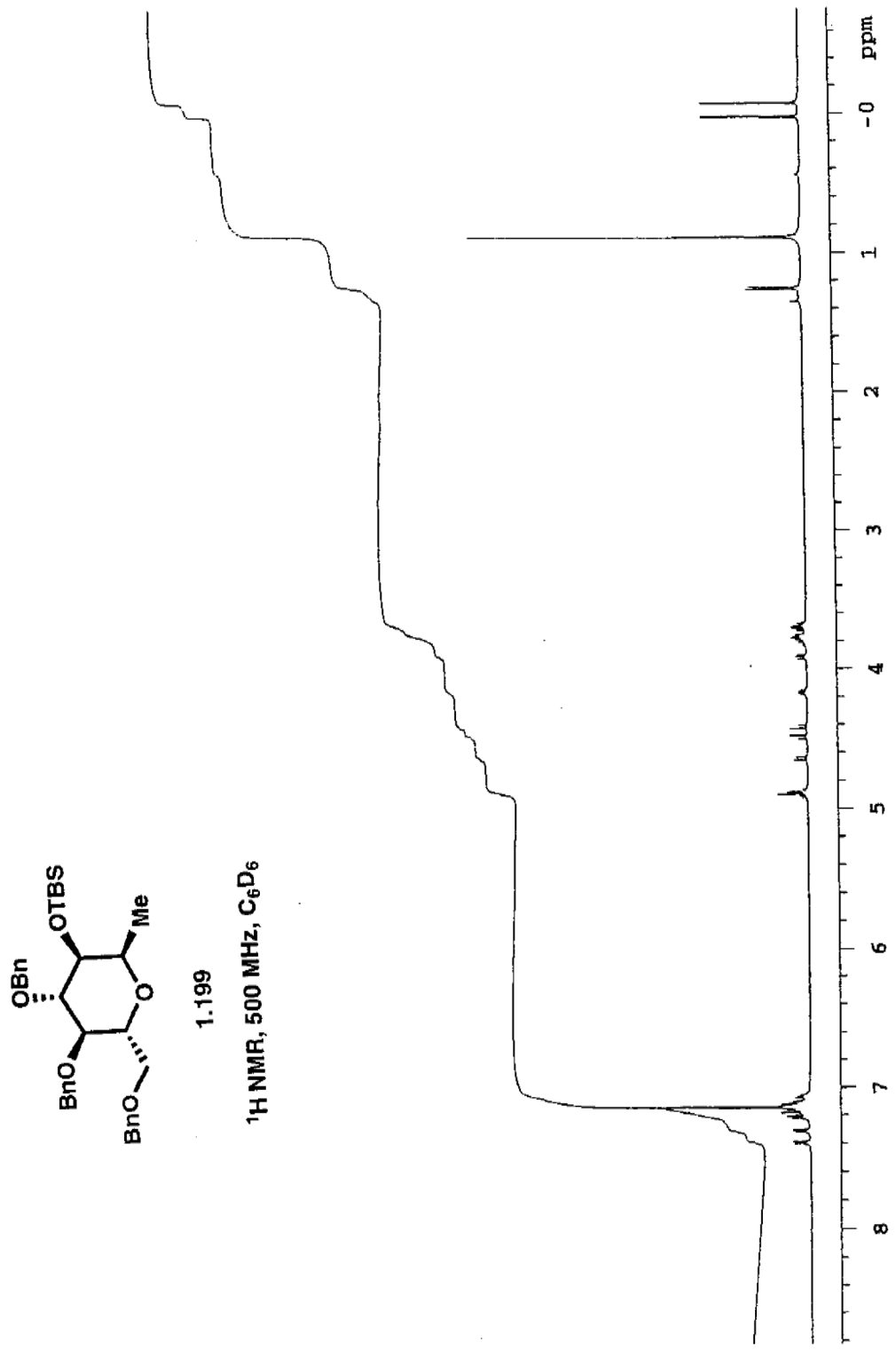
1.143

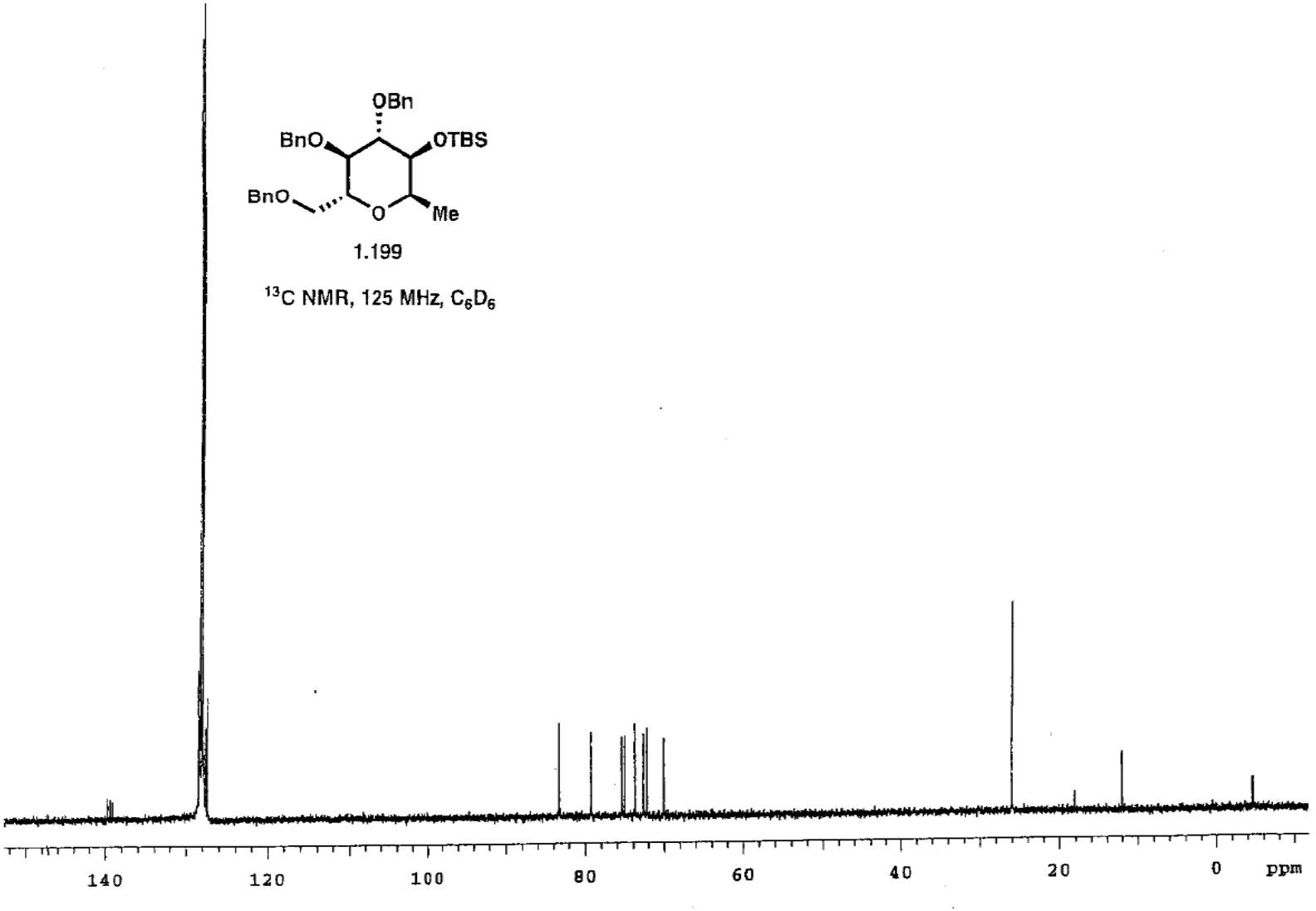
^{13}C NMR, 125 MHz, C_6D_6




Me
OTBS
OPMB
H
HO
O
H
H
1.148
^{1}H NMR, 500 MHz, C_6D_6
ppm
1
2
3
4
5
6
7
8

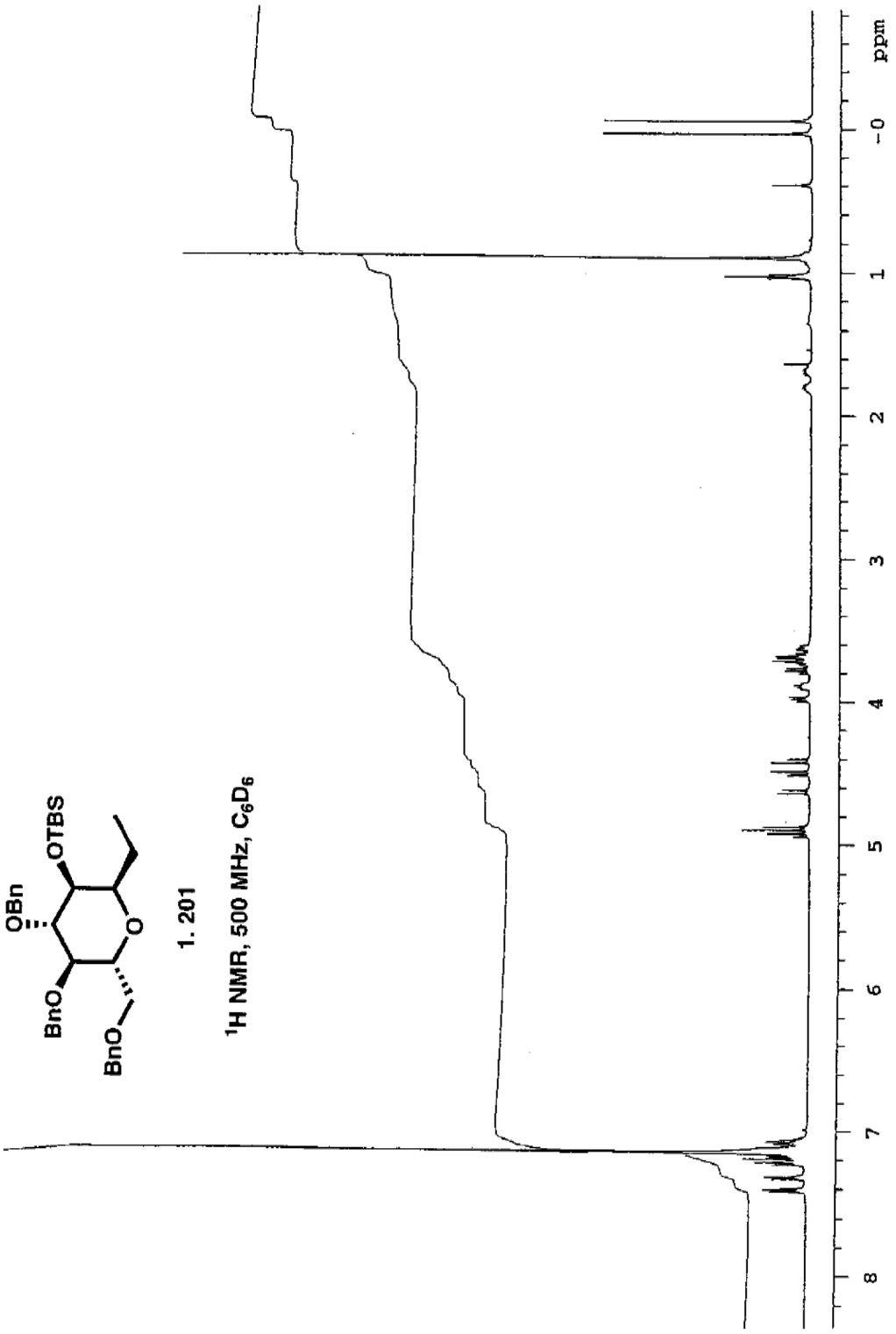

OPMB
OTBS
Me
HO
H
O
H
H
1.148
^{13}C NMR, 125 MHz, C_6D_6
ppm
0
20
40
60
80
100
120
140
160

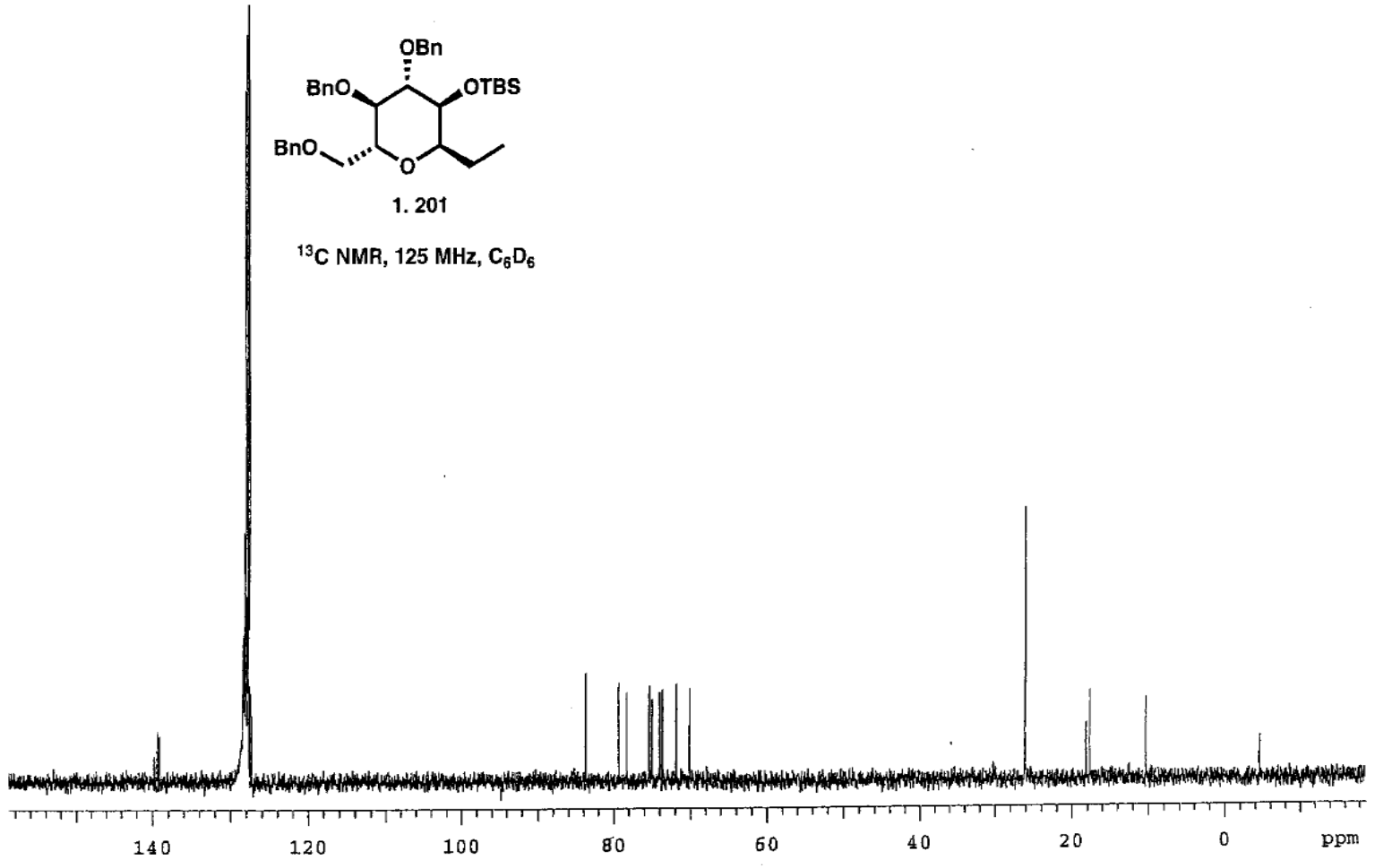

OBn
OTBS
Me
BnO
BnO
O
1.199
^{1}H NMR, 500 MHz, C_6D_6
ppm
8
7
6
5
4
3
2
1
0

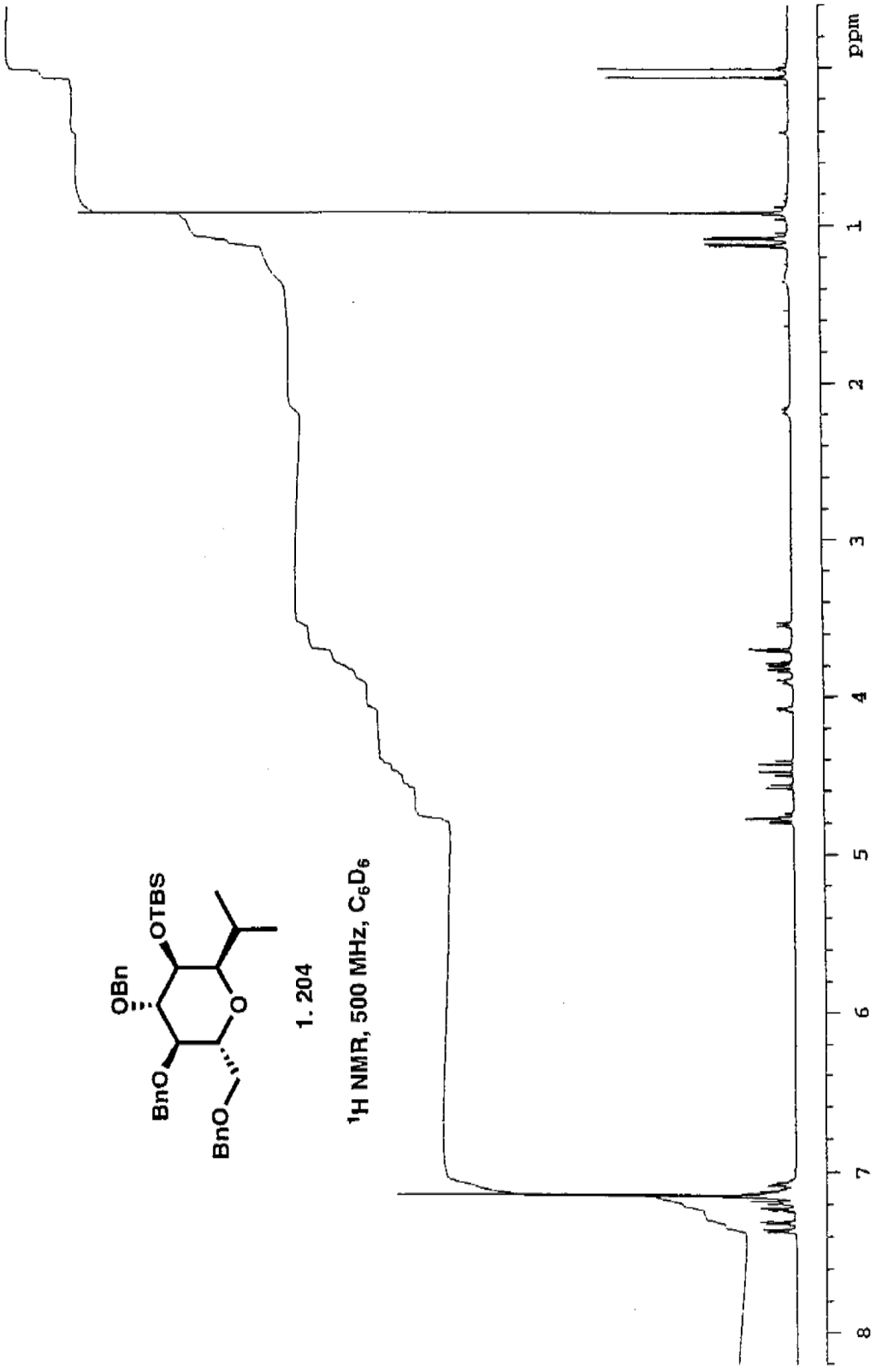


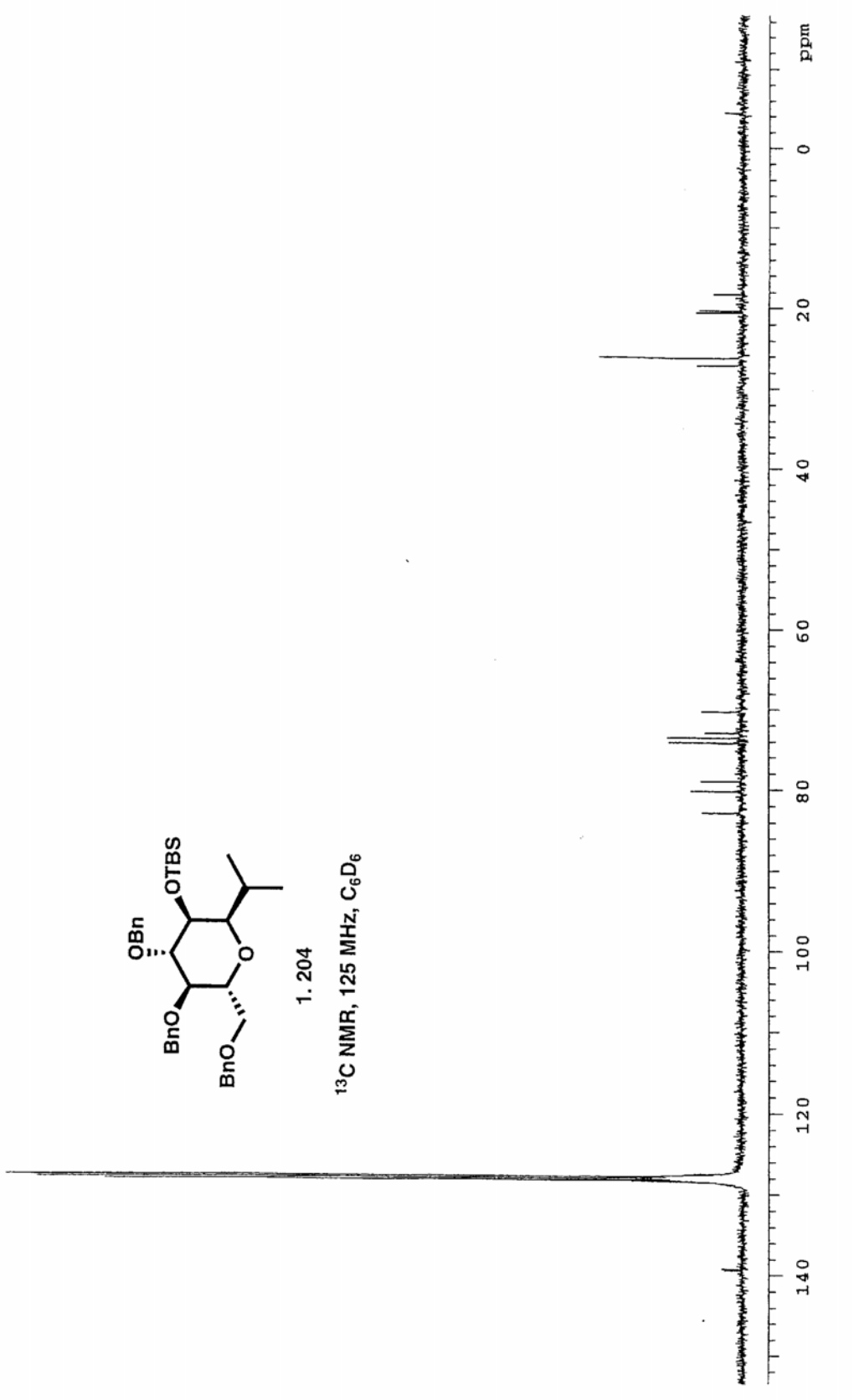
1.199

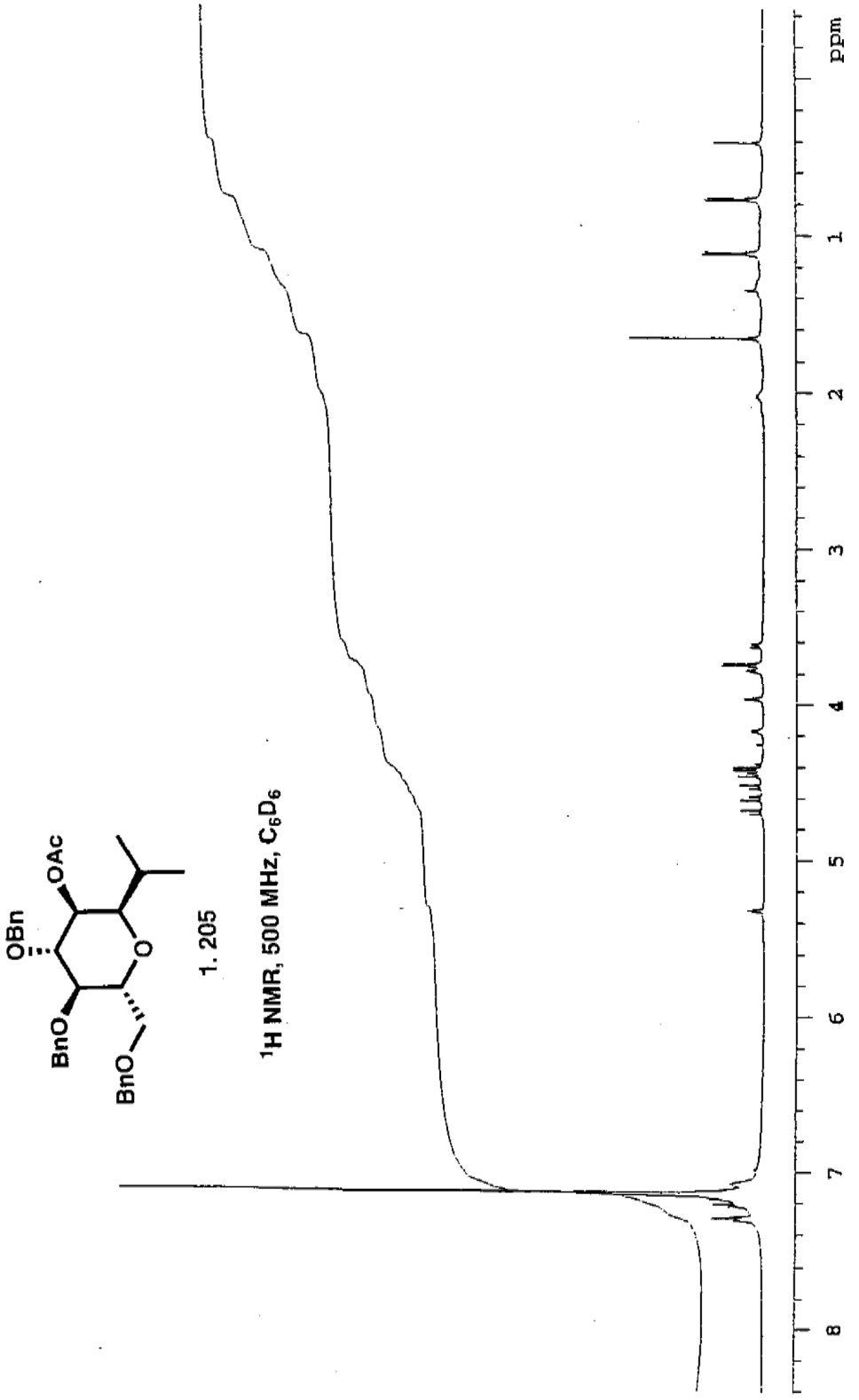
^{13}C NMR, 125 MHz, C_6D_6

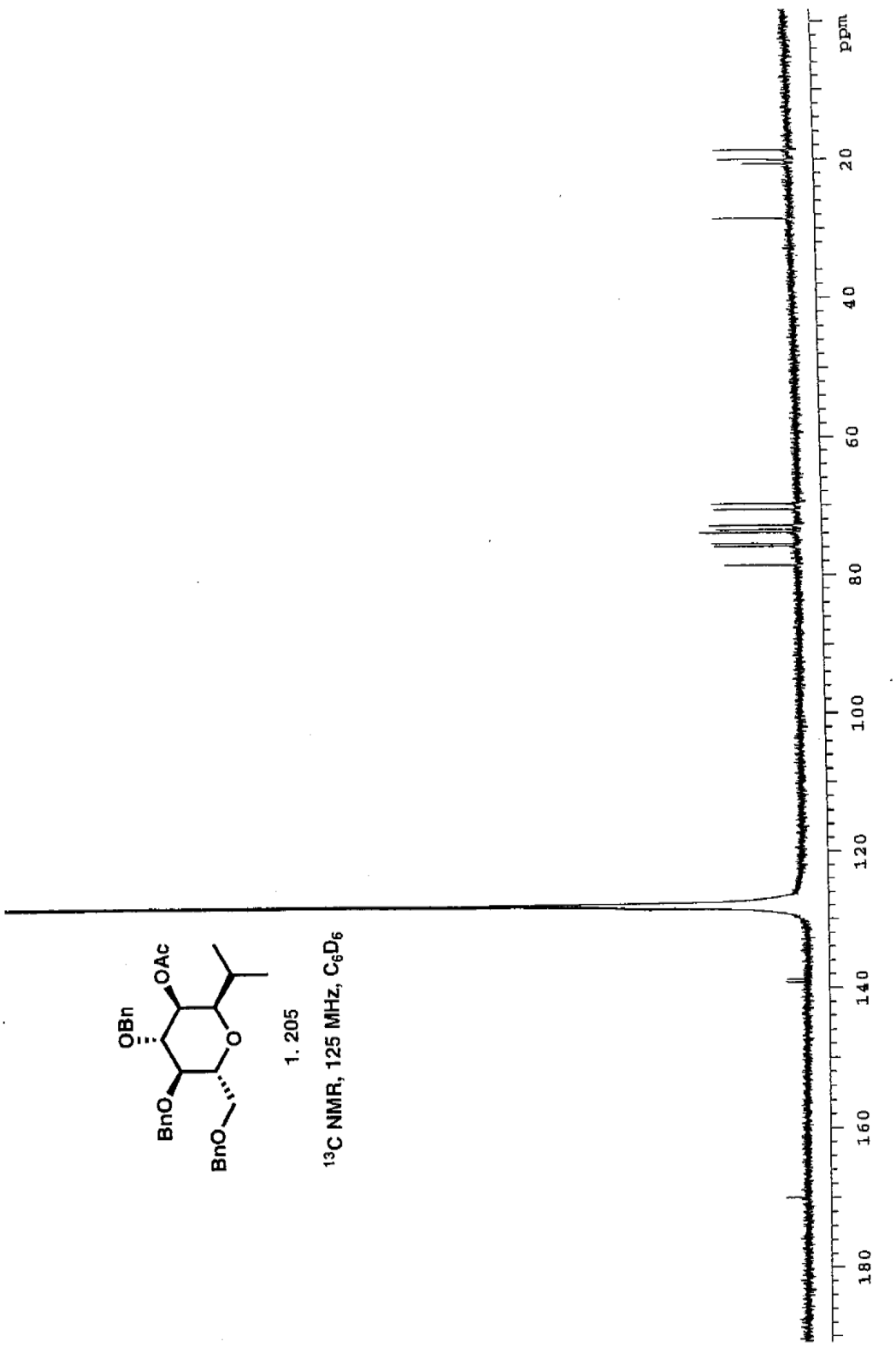

OBn
OTBS
BnO
BnO
1. 201
^{1}H NMR, 500 MHz, C_6D_6
ppm
8
7
6
5
4
3
2
1
0

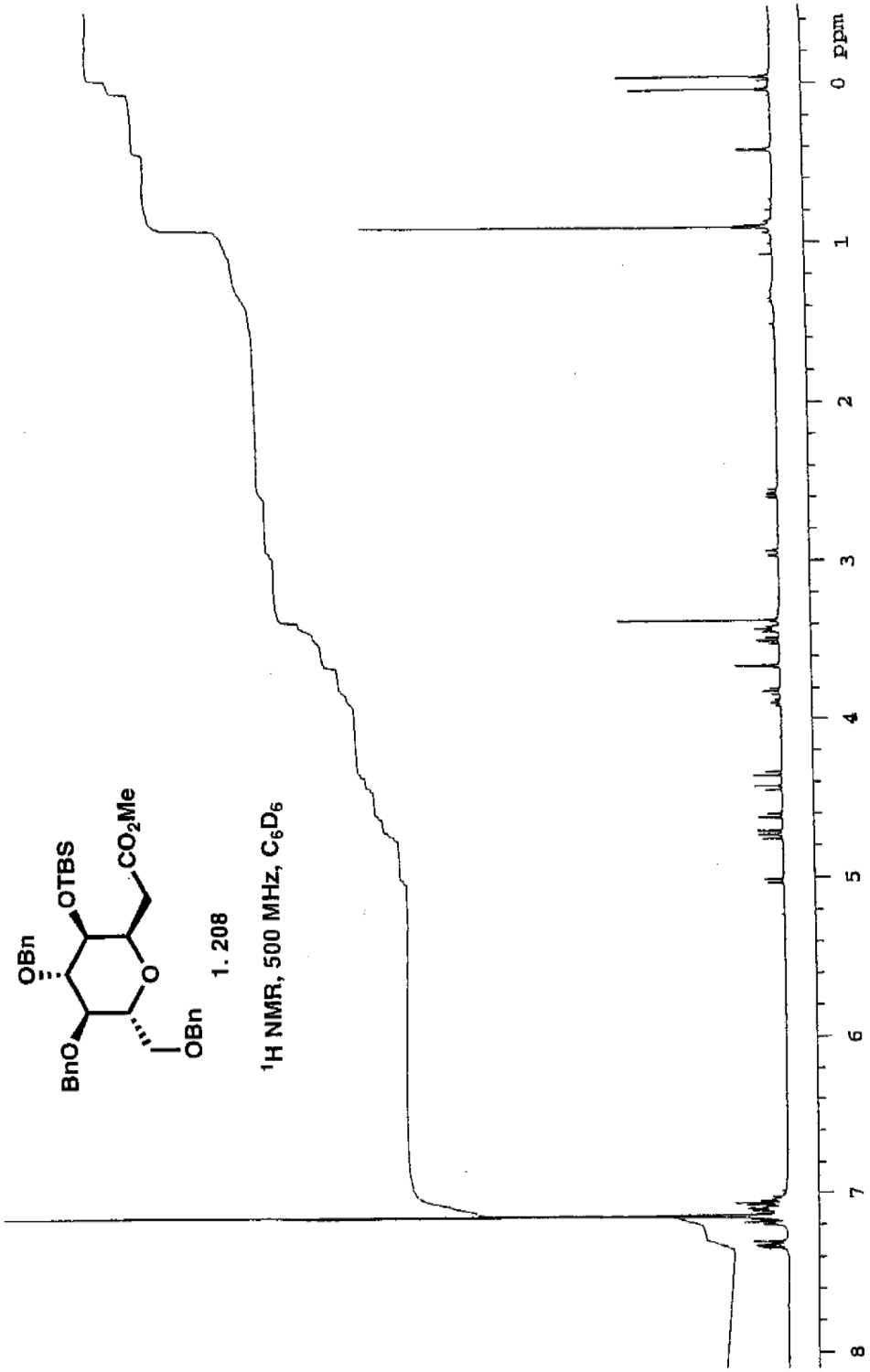

OBn
BnO
OTBS
BnO
O
1. 201
^{13}C NMR, 125 MHz, C_6D_6
140
120
100
80
60
40
20
0
ppm

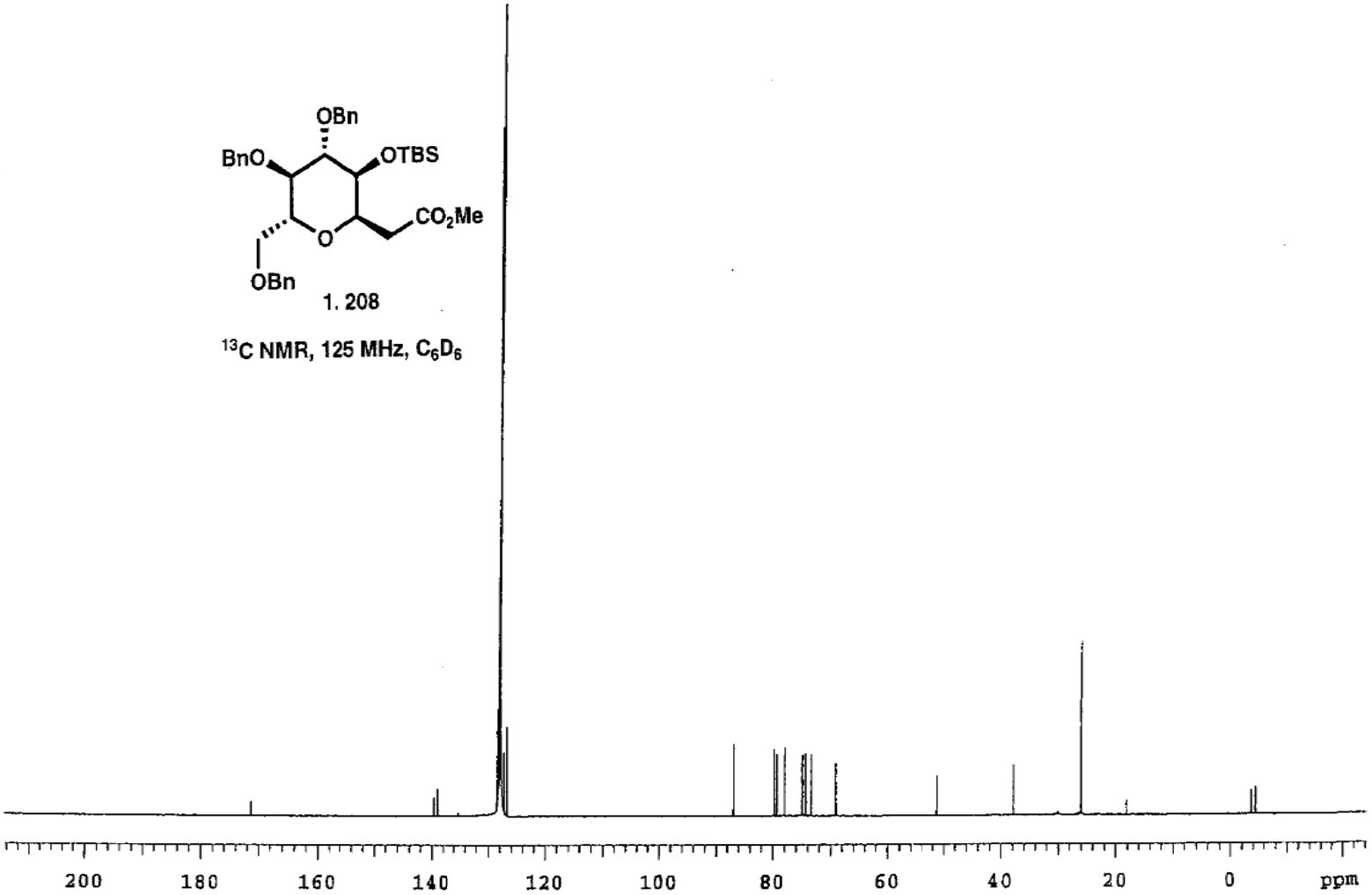

OTBS
OBn
BnO
BnO
O
1. 204
^{1}H NMR, 500 MHz, C_6D_6
ppm
1
2
3
4
5
6
7
8


OBn
OTBS
BnO
BnO
O
1. 204
^{13}C NMR, 125 MHz, C_6D_6
ppm
0
20
40
60
80
100
120
140


OBn
OAc
BnO
BnO
1. 205
^{1}H NMR, 500 MHz, C_6D_6
ppm
1
2
3
4
5
6
7
8

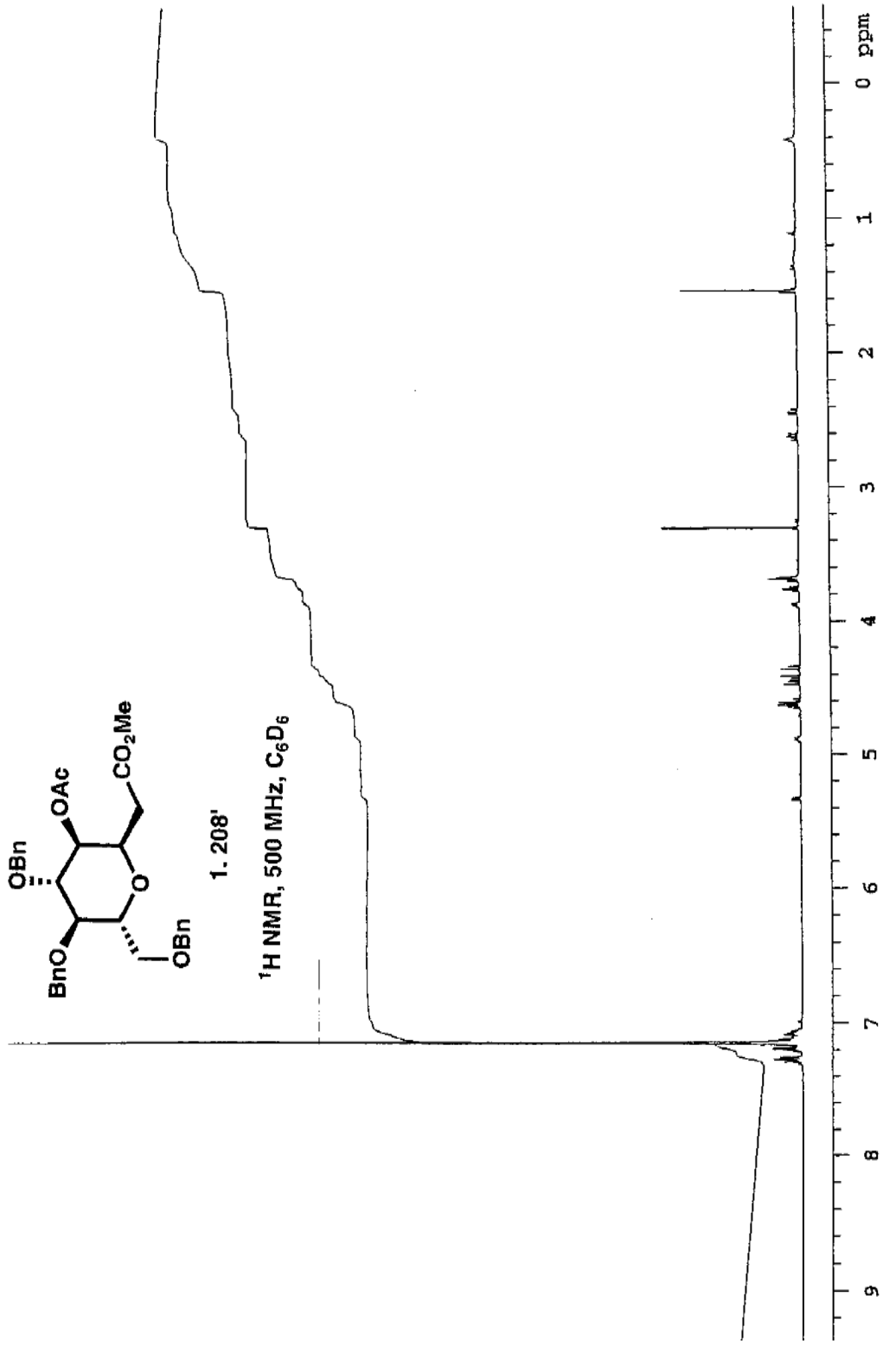

OBn
OAc
BnO
BnO
O
1. 205
^{13}C NMR, 125 MHz, C_6D_6
ppm
180
160
140
120
100
80
60
40
20

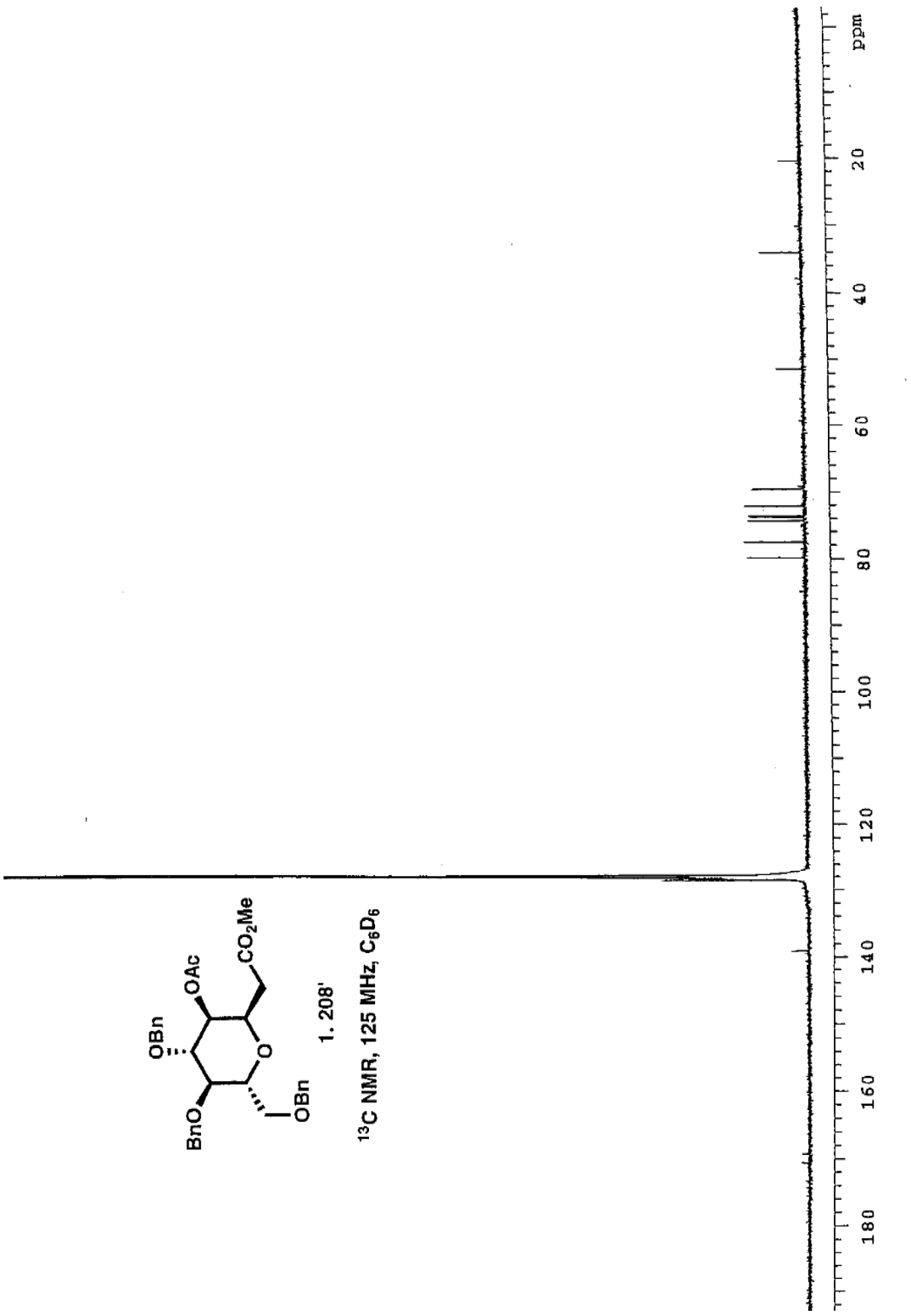

OBn
OTBS
CO2Me
BnO
OBn
O
1. 208
1H NMR, 500 MHz, C6D6
0 ppm
1
2
3
4
5
6
7
8

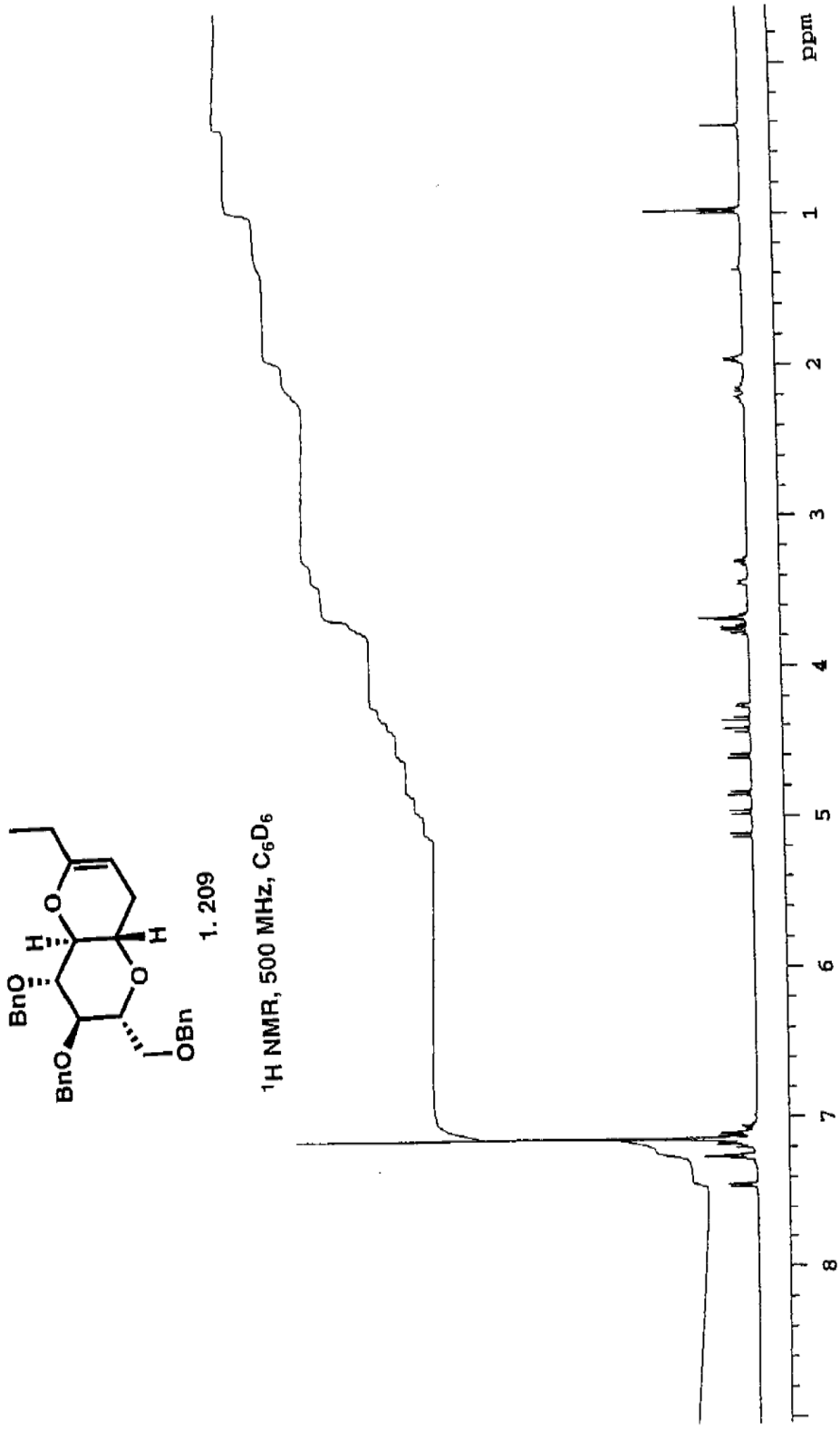


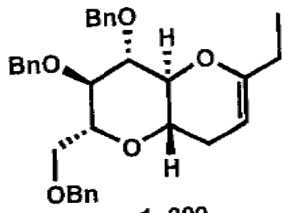
1. 208

^{13}C NMR, 125 MHz, C_6D_6


OBn
OAc
CO2Me
BnO
OBn
O
1. 208'
1H NMR, 500 MHz, C6D6
9
8
7
6
5
4
3
2
1
0 ppm

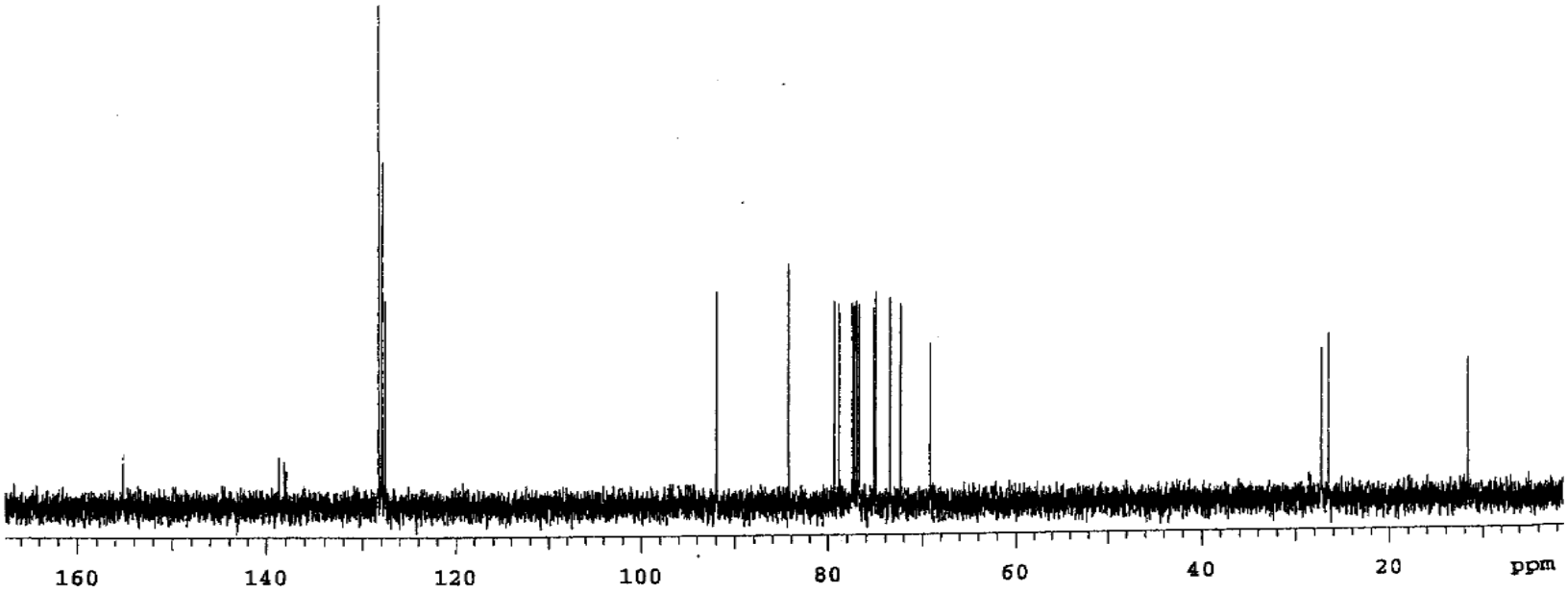

OBn
OAc
CO2Me
BnO
OBn
O
1. 208'
13C NMR, 125 MHz, C6D6
ppm
180
160
140
120
100
80
60
40
20

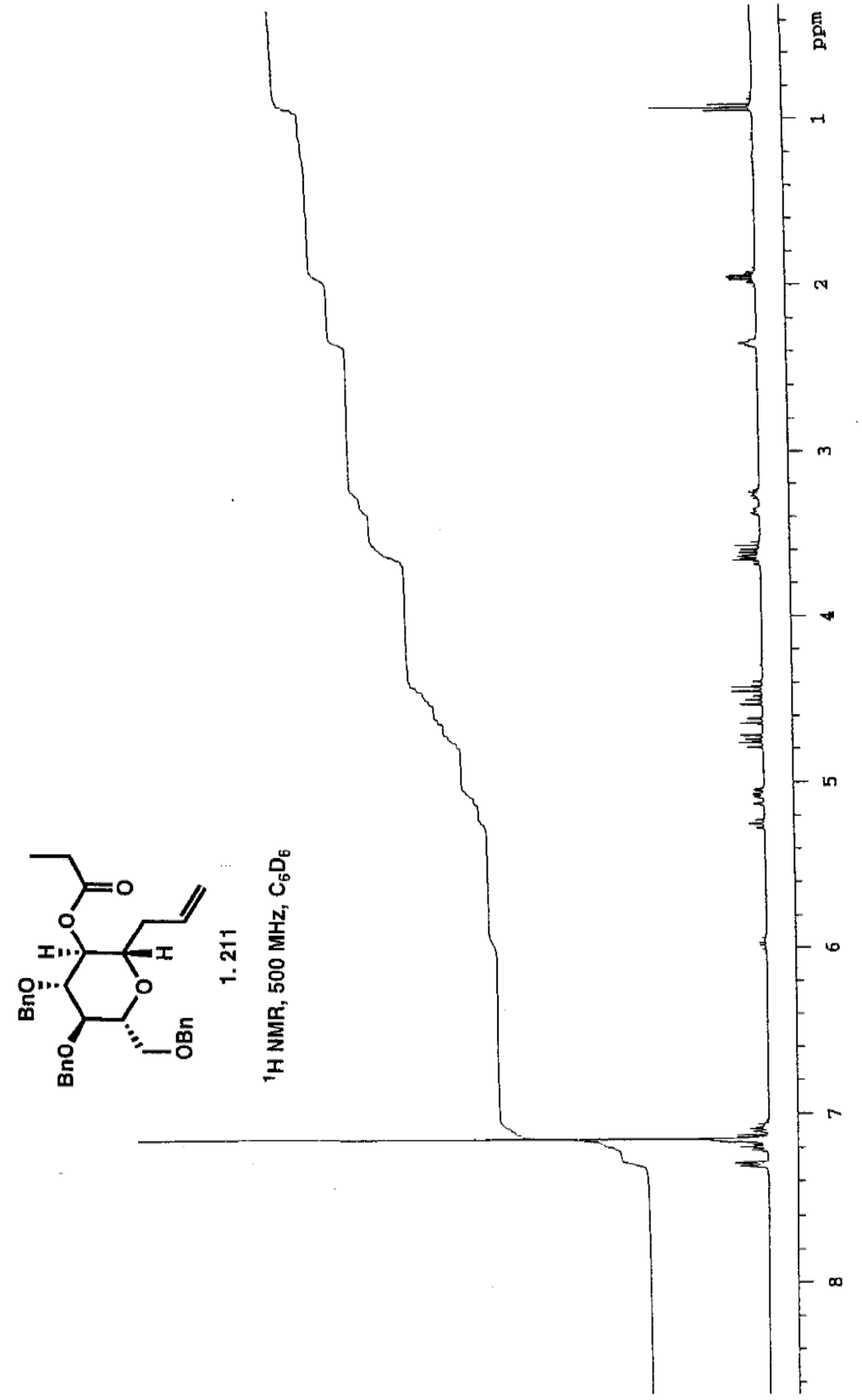

BnO
BnO
OBn
1. 209
^{1}H NMR, 500 MHz, C_6D_6
ppm
1
2
3
4
5
6
7
8

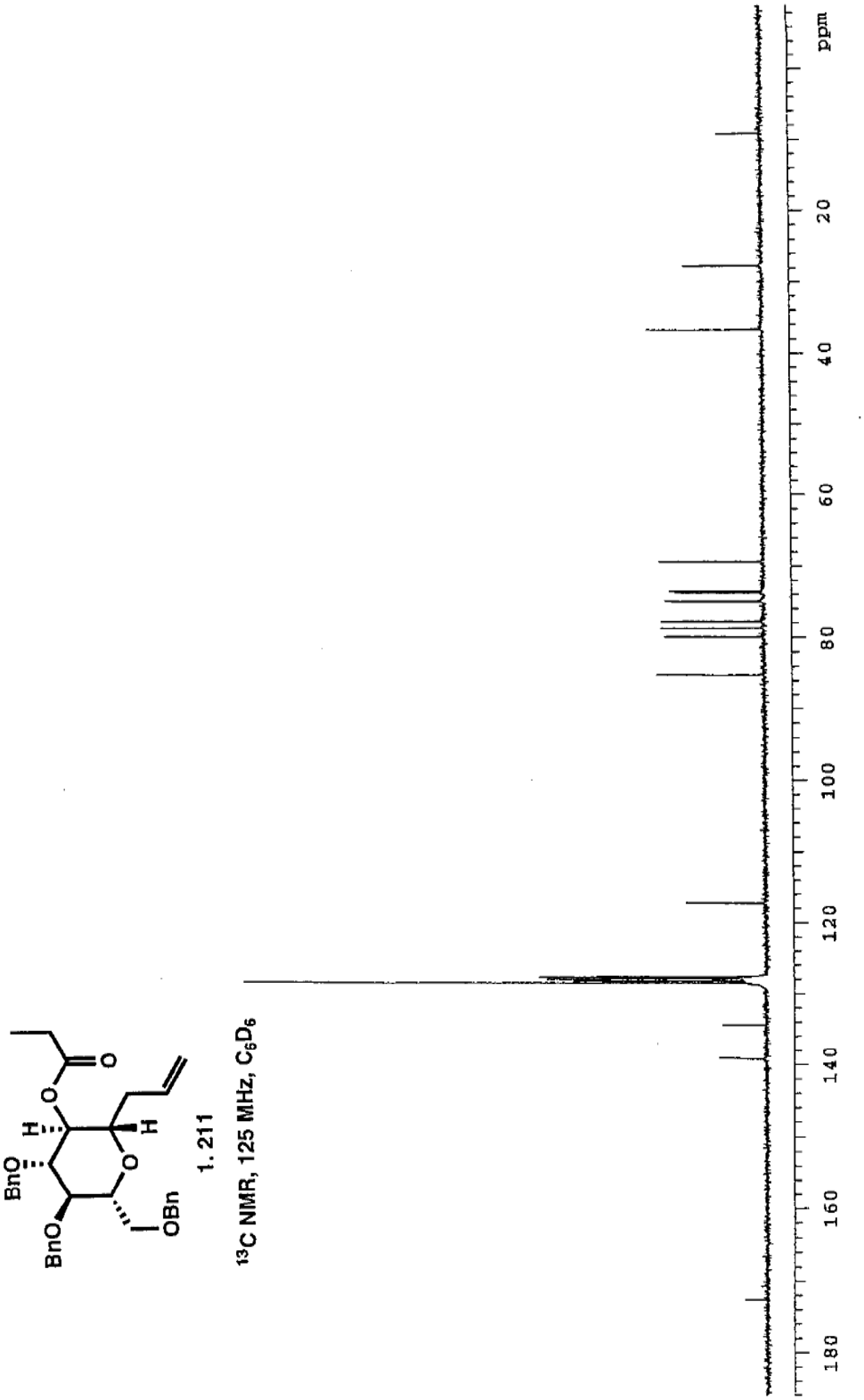


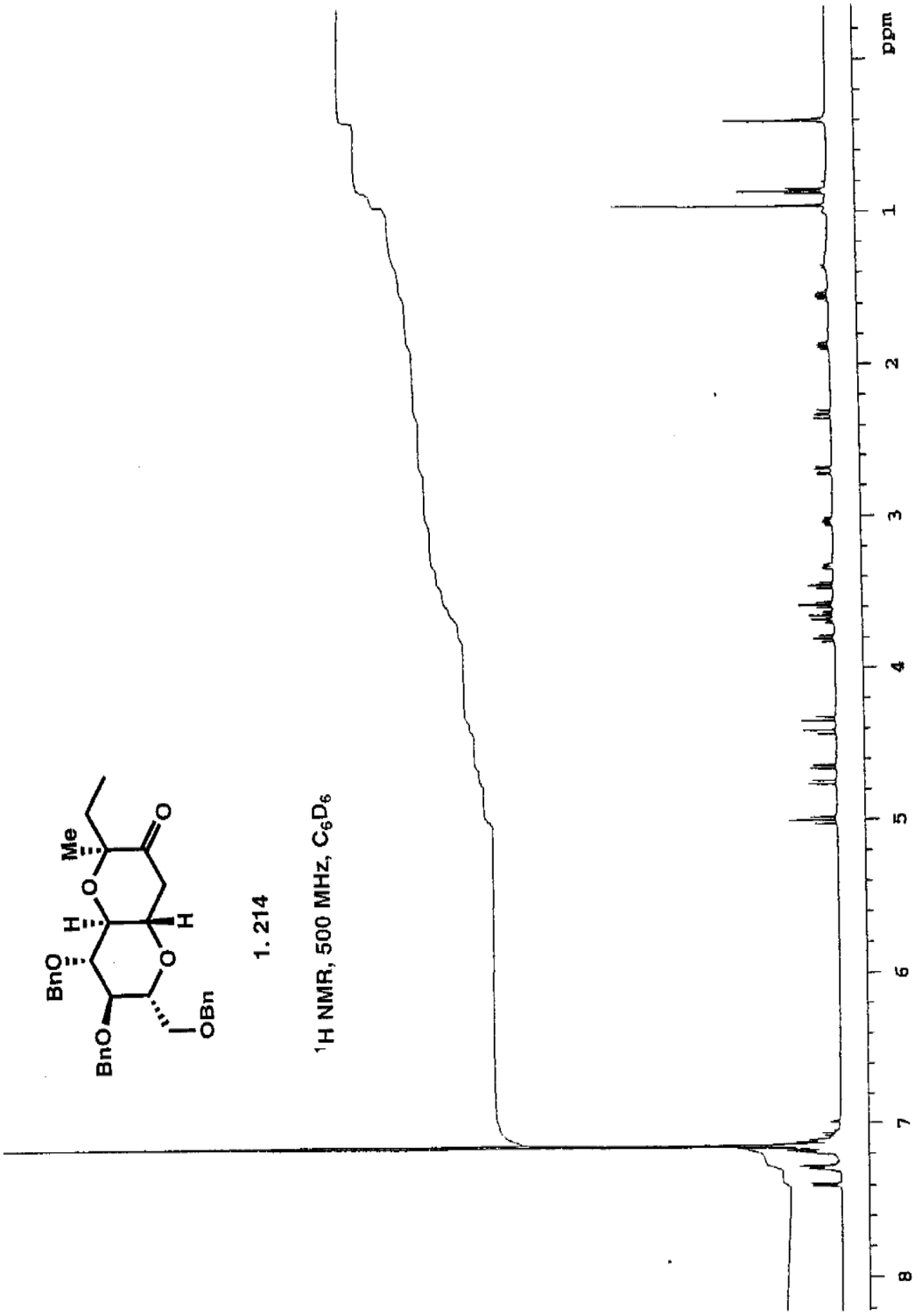
1. 209

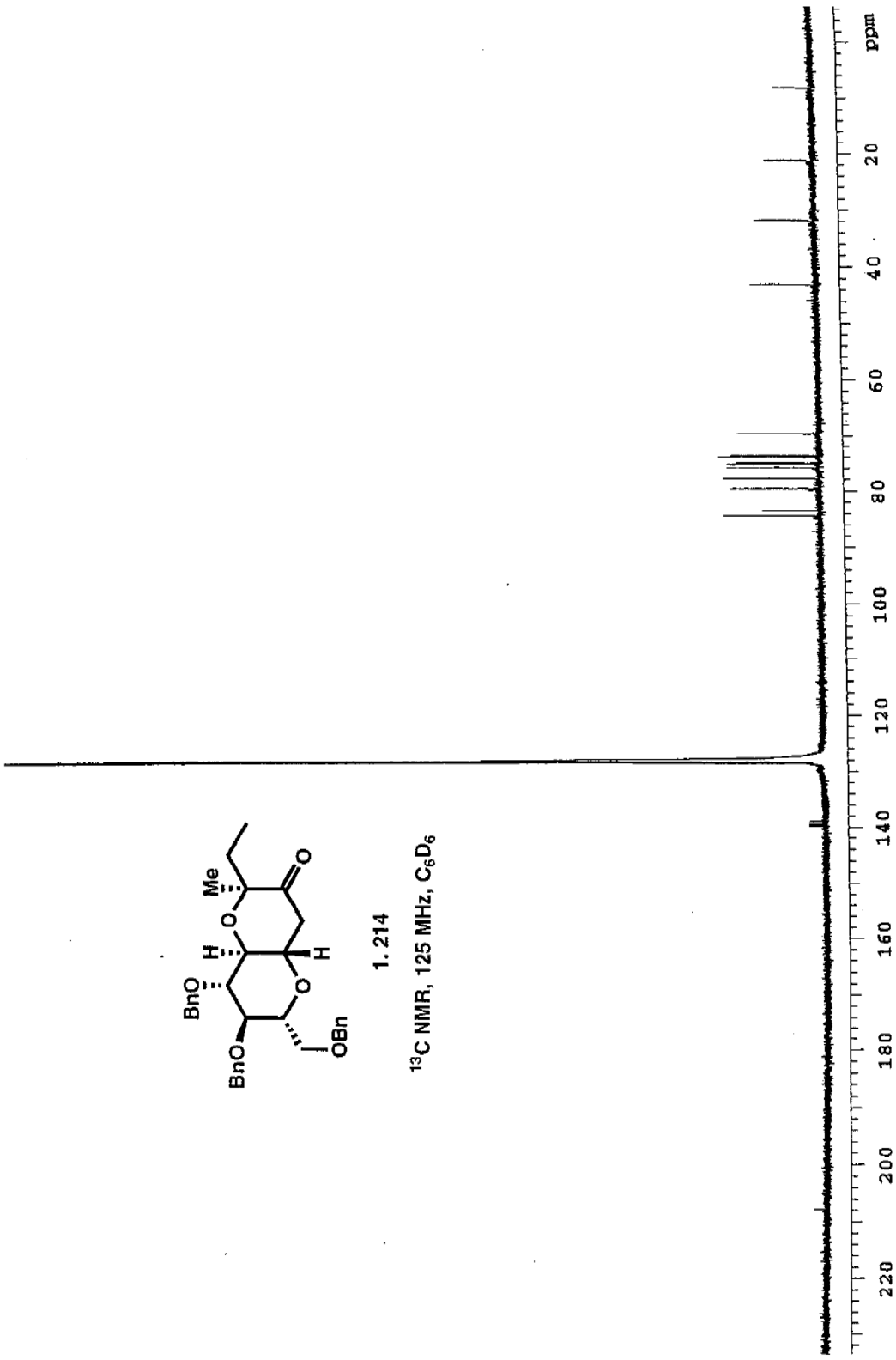
^{13}C NMR, 125 MHz, $CDCl_3$

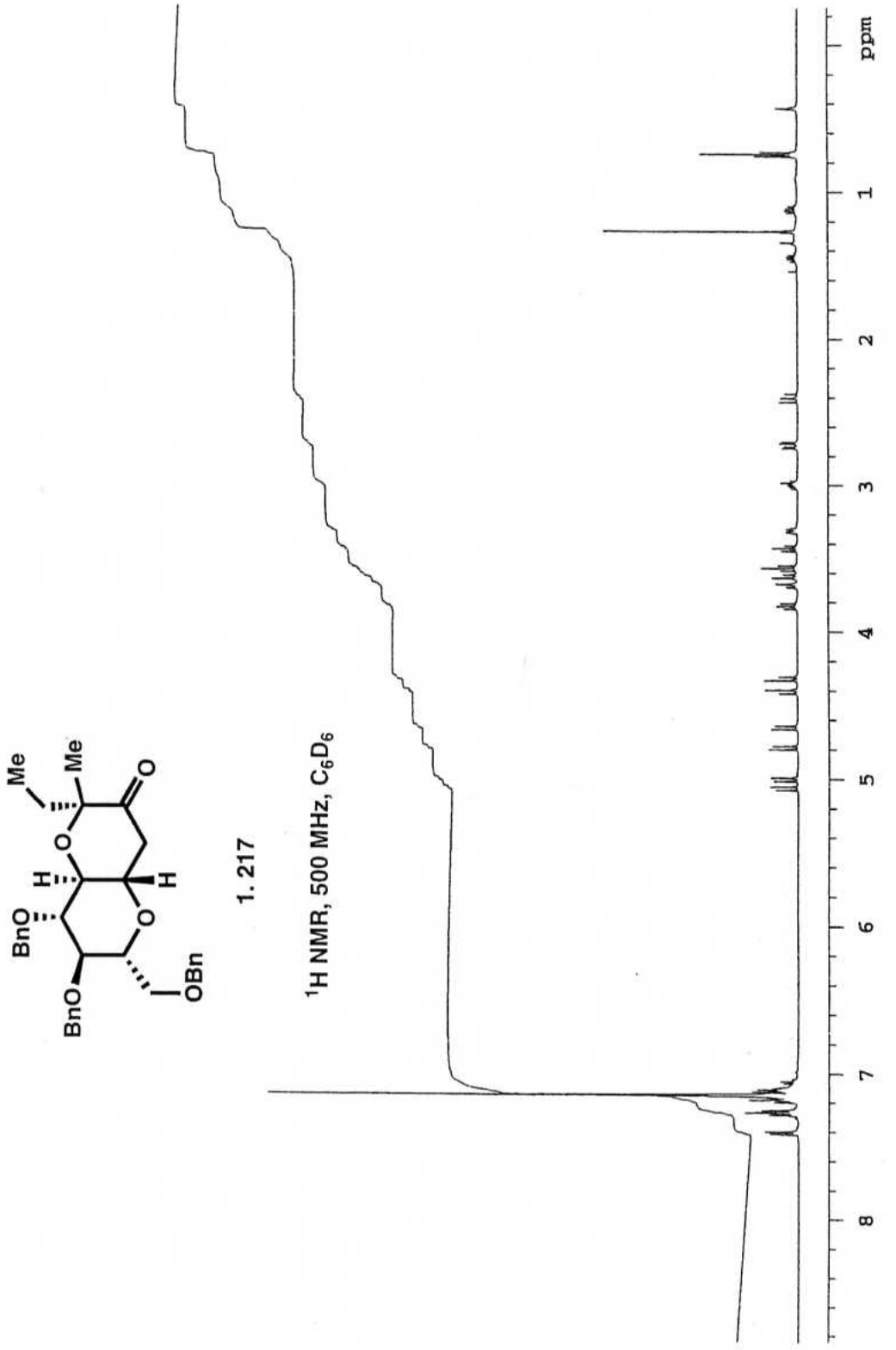


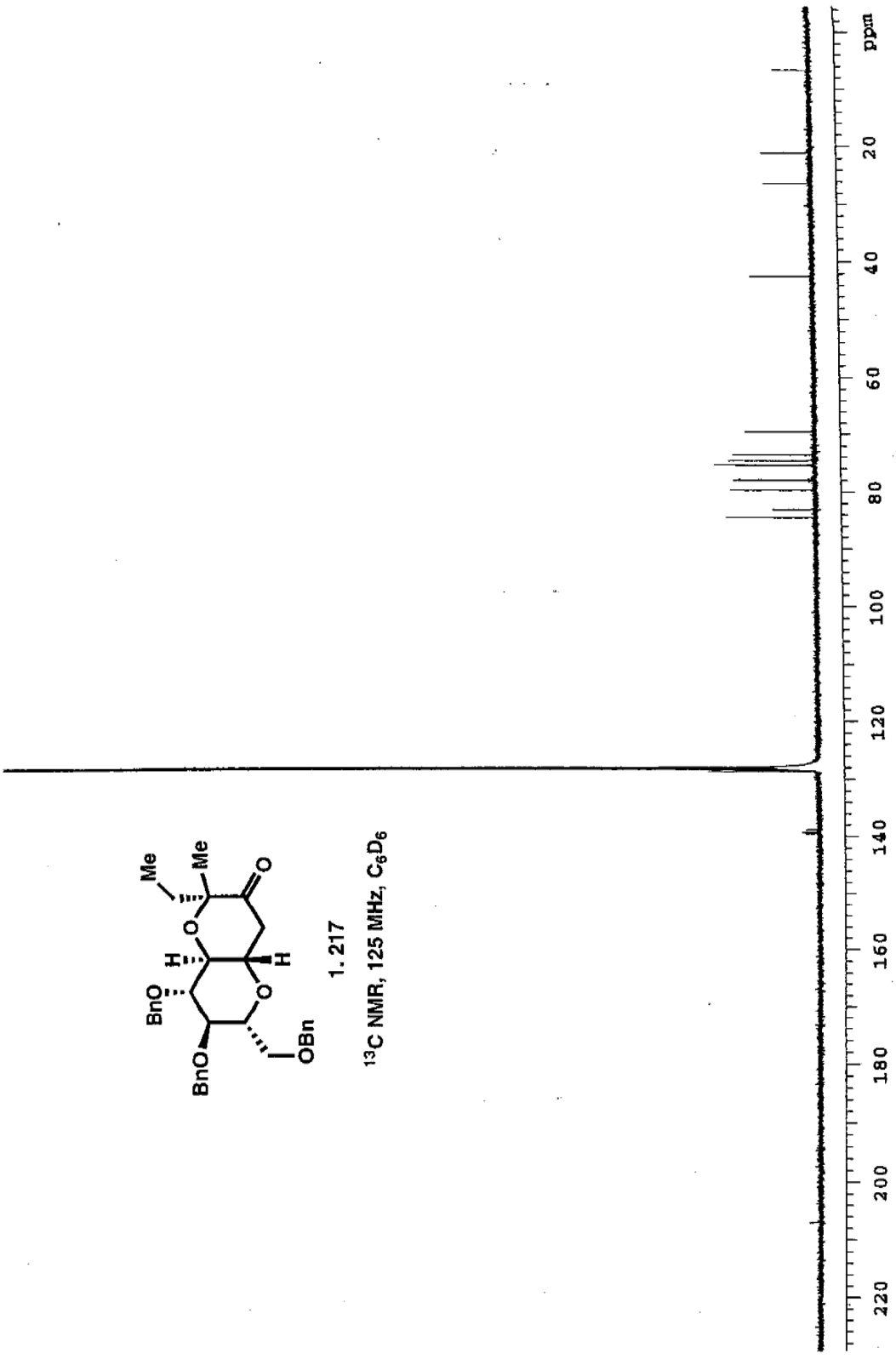

BnO
BnO
OBn
1. 211
^{1}H NMR, 500 MHz, C_6D_6
ppm
1
2
3
4
5
6
7
8

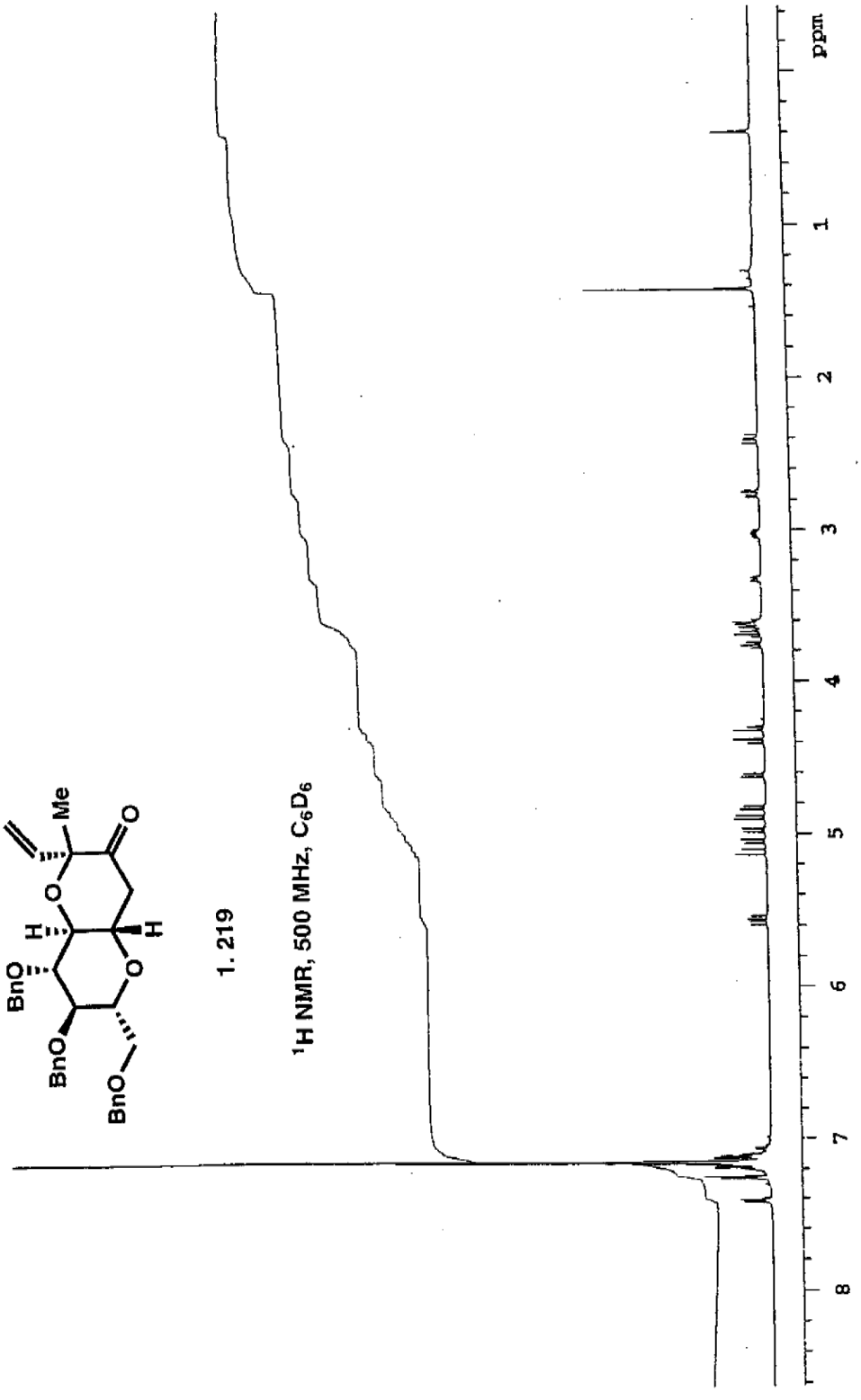

BnO
BnO
OBn
O
O
O
H
H
1.211
^{13}C NMR, 125 MHz, C_6D_6
ppm
180
160
140
120
100
80
60
40
20

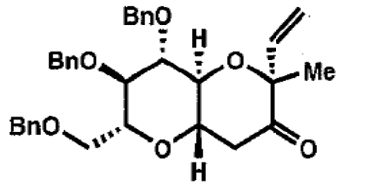

Me
O
O
H
H
BnO
O
BnO
OBn
1. 214
^{1}H NMR, 500 MHz, C_6D_6
ppm
1
2
3
4
5
6
7
8


Me
O
H
H
O
BnO
BnO
OBn
O
1.214
^{13}C NMR, 125 MHz, C_6D_6
ppm
220
200
180
160
140
120
100
80
60
40
20


Me
Me
O
H
H
BnO
BnO
OBn
O
O
1. 217
^{1}H NMR, 500 MHz, C_6D_6
ppm
1
2
3
4
5
6
7
8

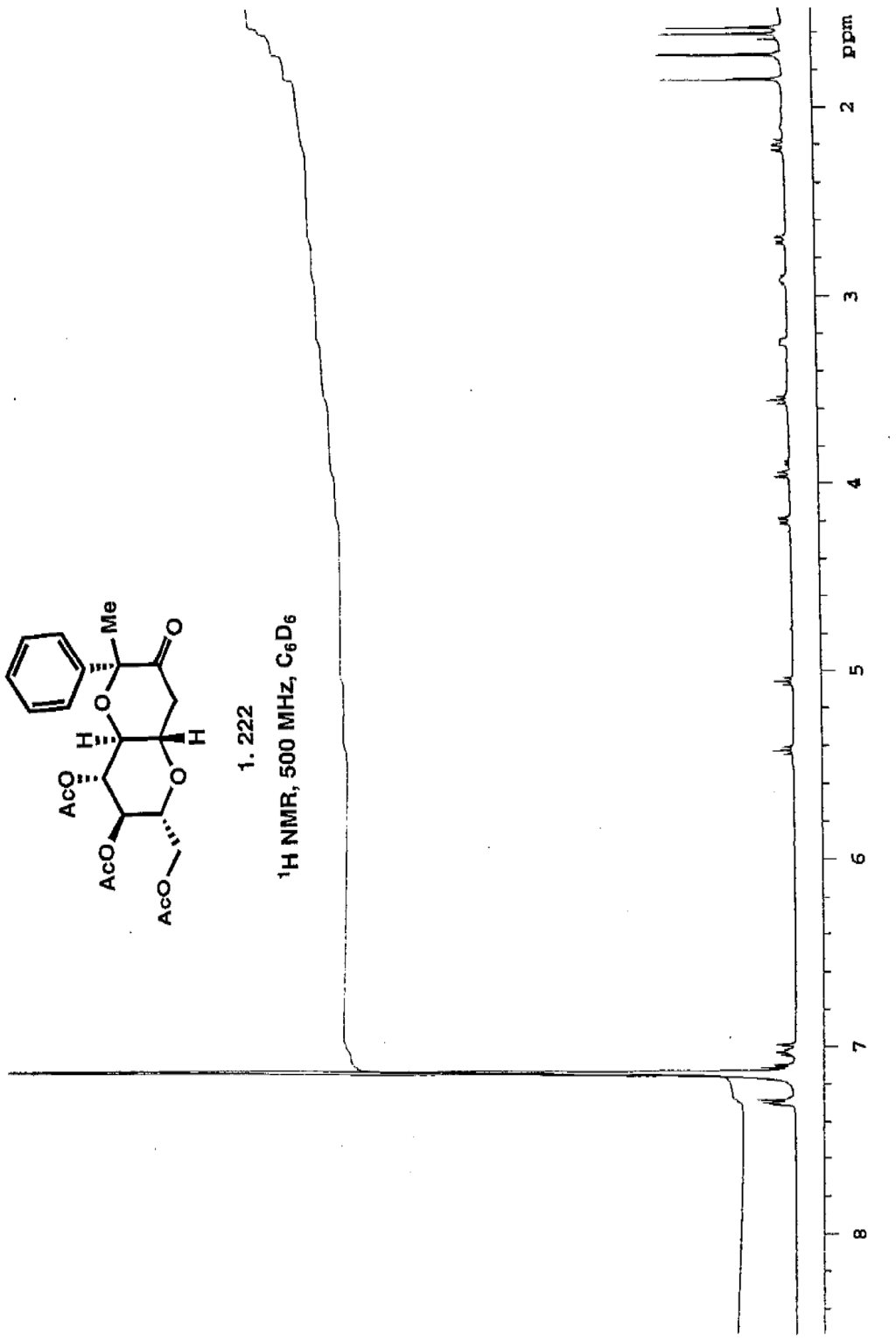

Me
Me
O
O
H
H
O
BnO
BnO
OBn
1. 217
^{13}C NMR, 125 MHz, C_6D_6
ppm
220
200
180
160
140
120
100
80
60
40
20

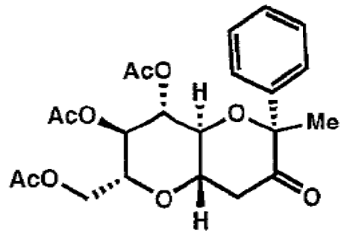

Me
O
O
H
H
O
BnO
BnO
BnO
1. 219
^{1}H NMR, 500 MHz, C_6D_6
ppm
1
2
3
4
5
6
7
8



1. 219

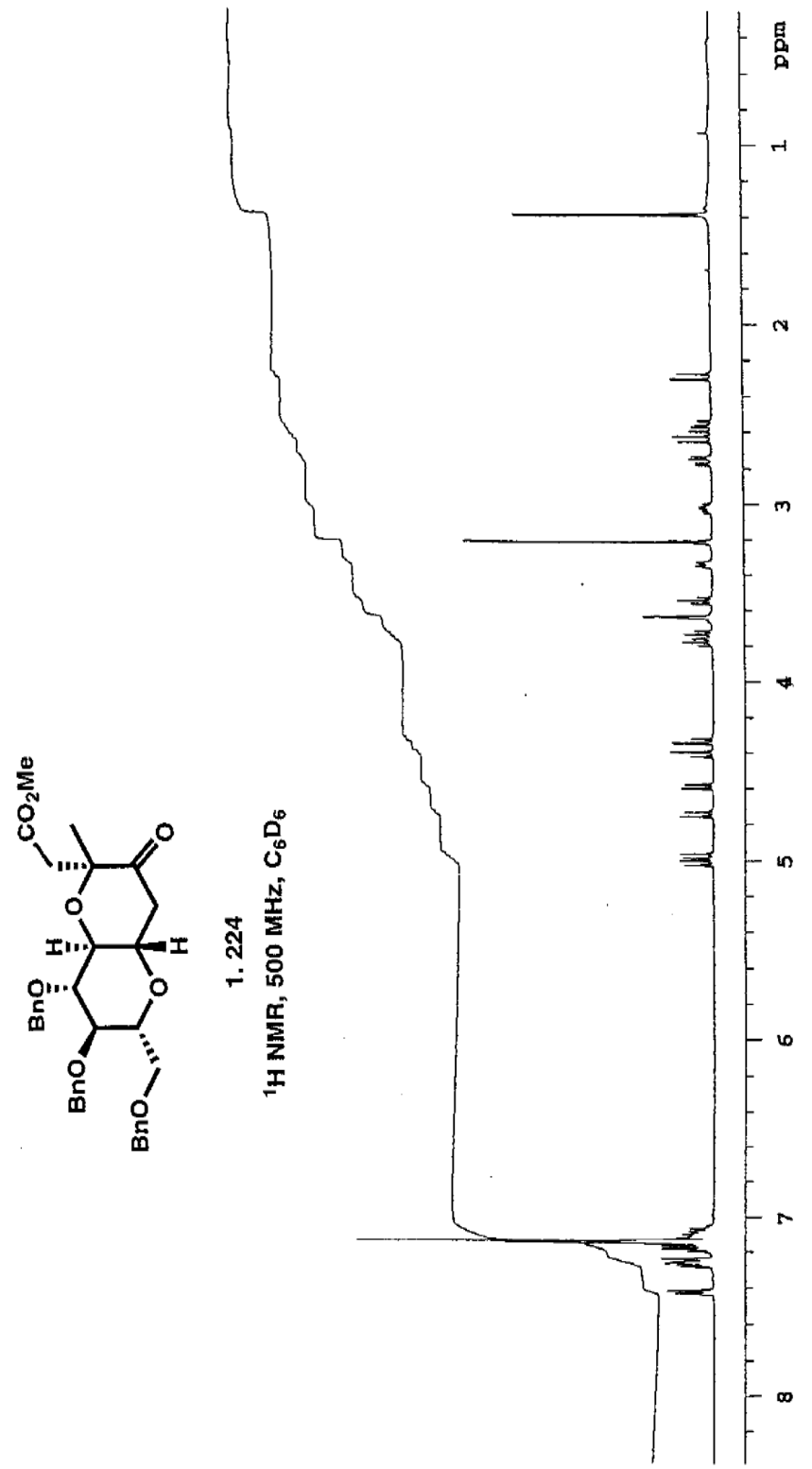
^{13}C NMR, 125 MHz, C_6D_6

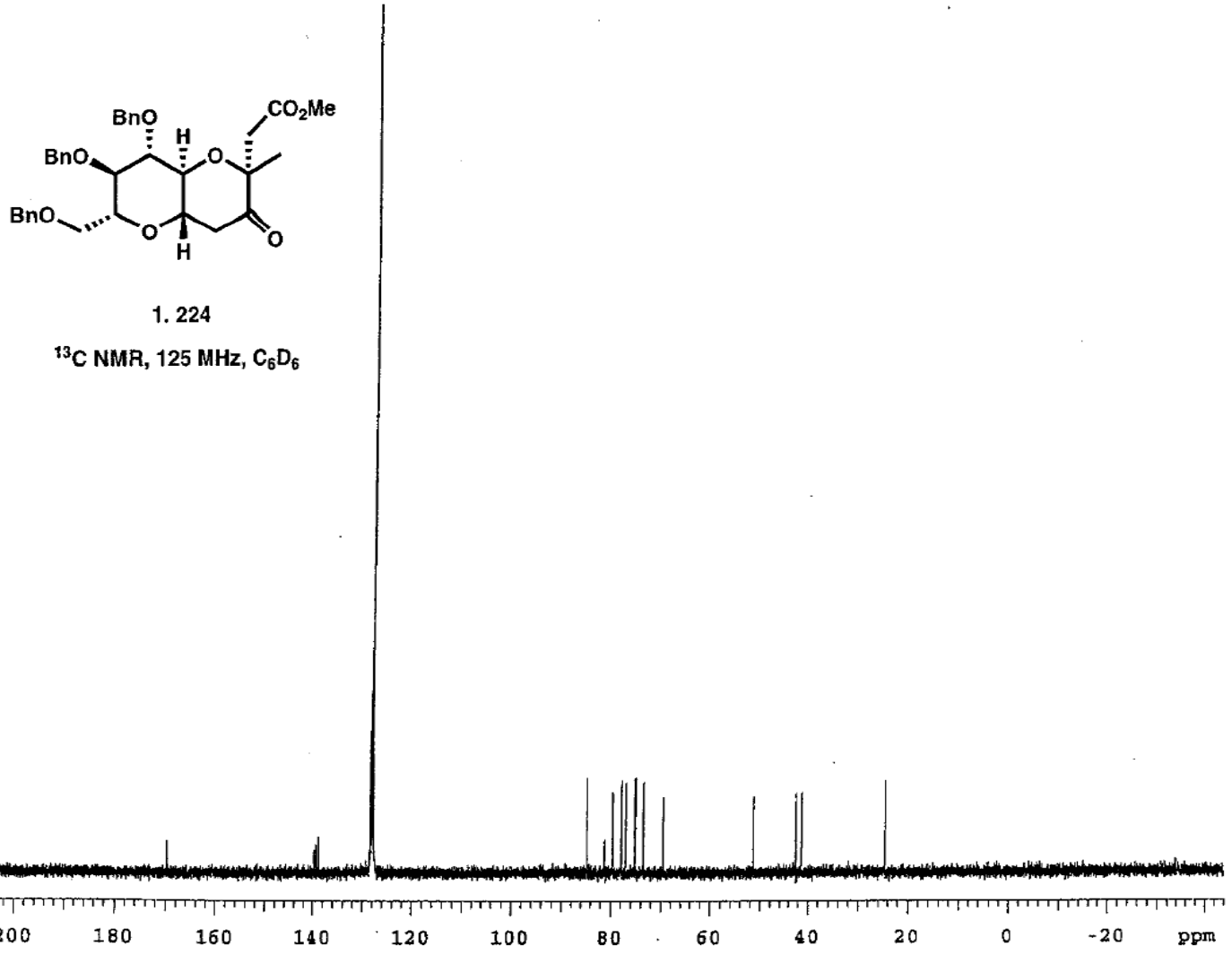

Me
O
O
H
H
O
AcO
AcO
AcO
1. 222
^{1}H NMR, 500 MHz, C_6D_6
ppm
2
3
4
5
6
7
8



1. 222

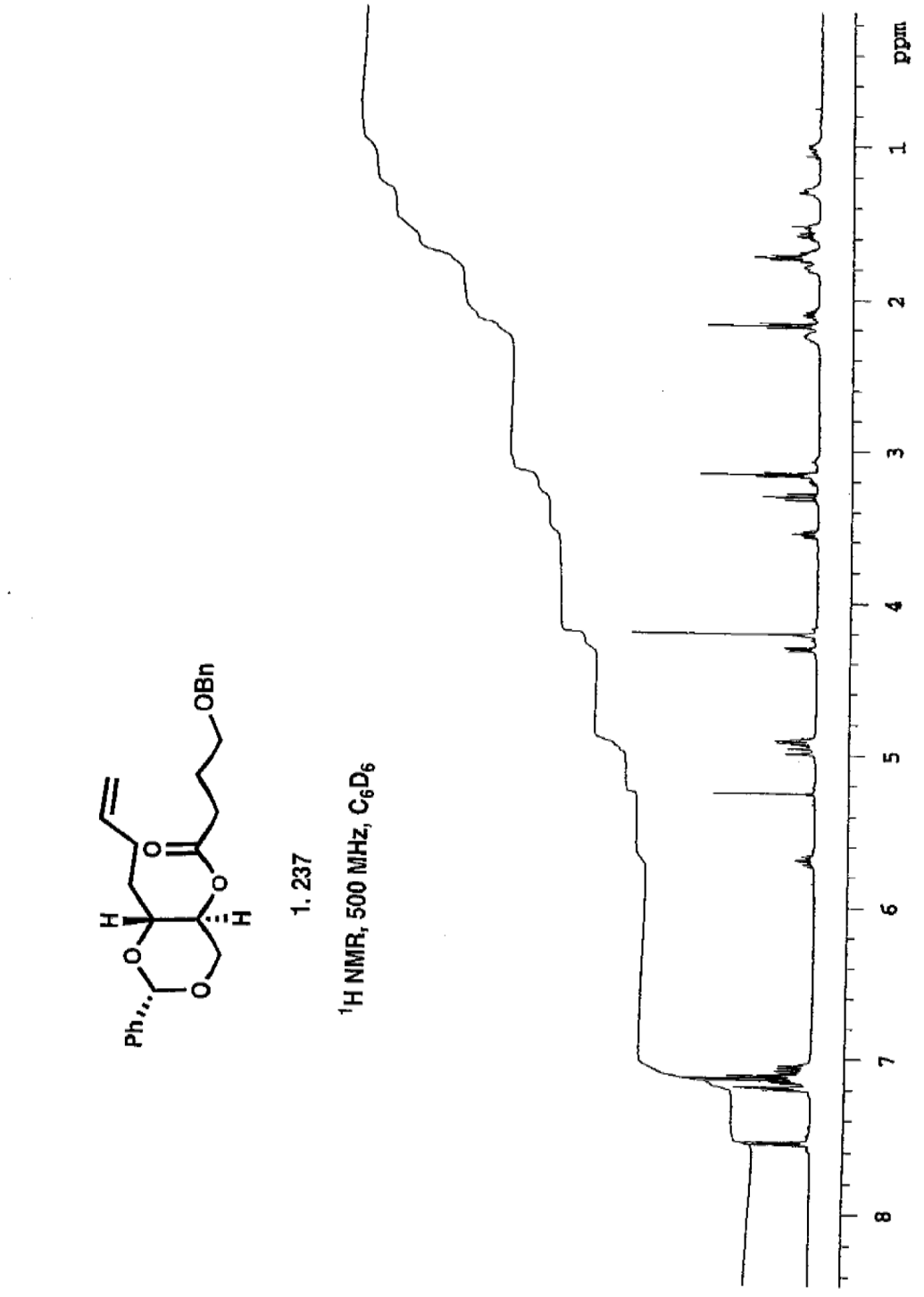
^{13}C NMR, 125 MHz, C_6D_6

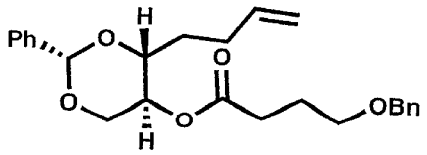

CO2Me
O
O
H
H
O
BnO
BnO
BnO
1. 224
1H NMR, 500 MHz, C6D6
ppm
1
2
3
4
5
6
7
8



1. 224

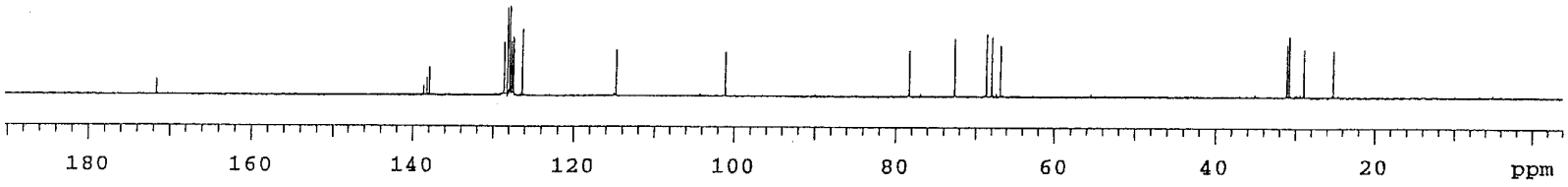
^{13}C NMR, 125 MHz, C_6D_6

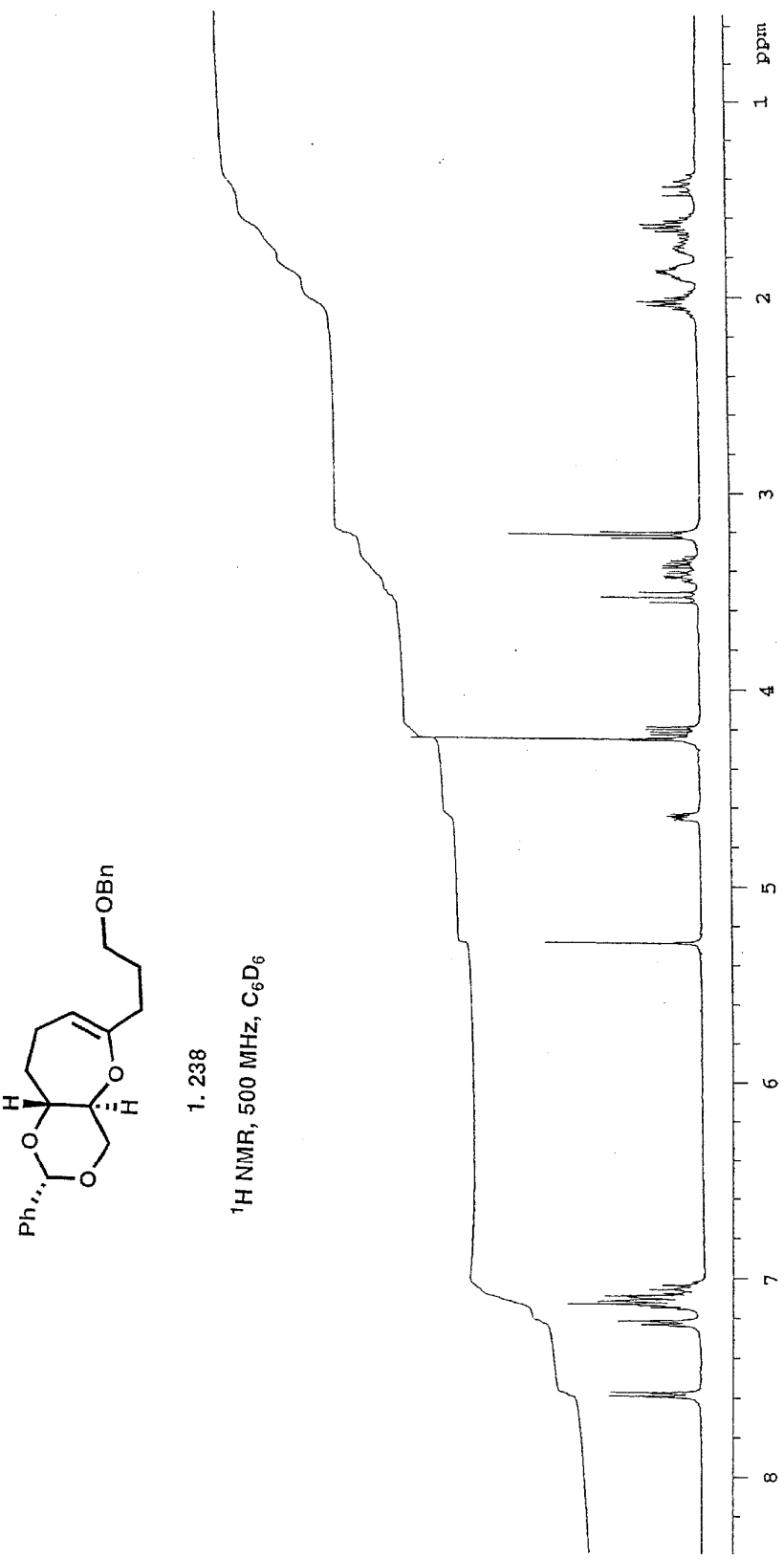

OBn
O
O
O
O
H
H
Ph
1. 237
^{1}H NMR, 500 MHz, C_6D_6
8
7
6
5
4
3
2
1
ppm

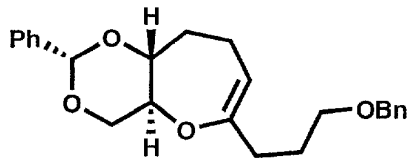


1. 237

^{13}C NMR, 125 MHz, C_6D_6

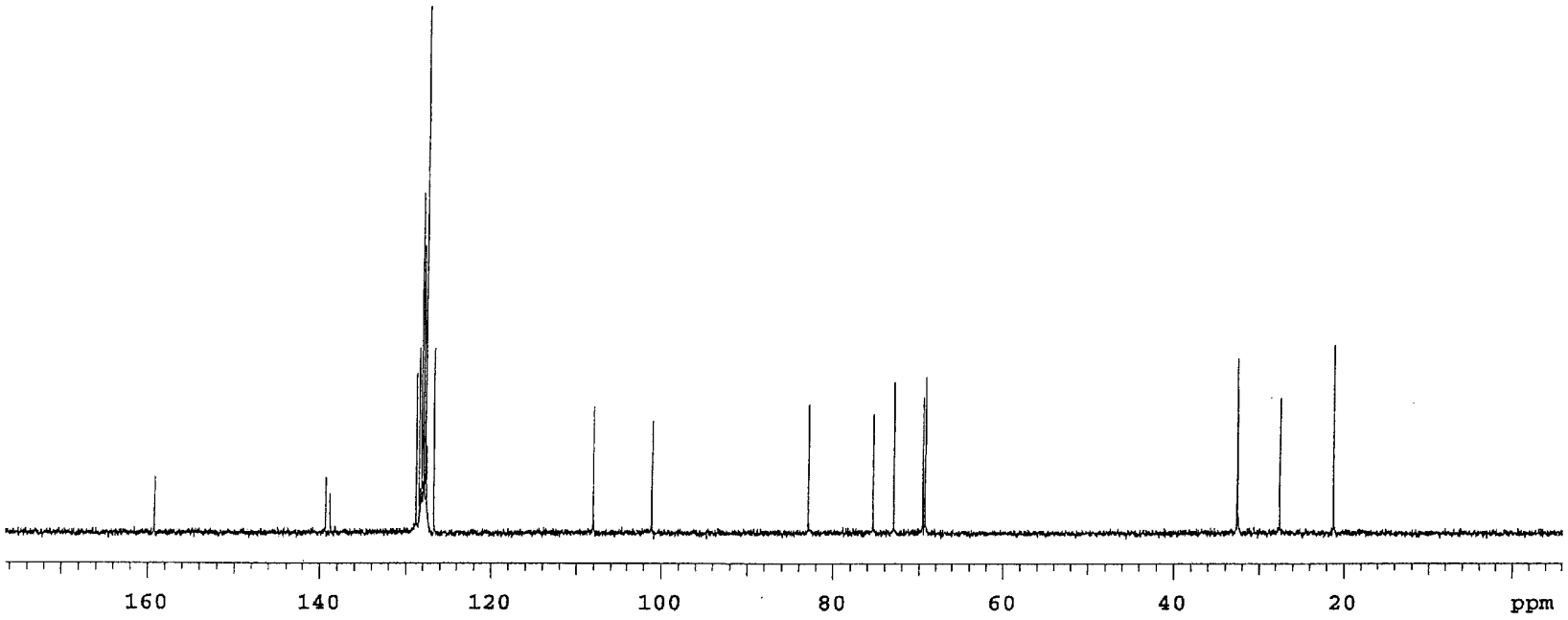


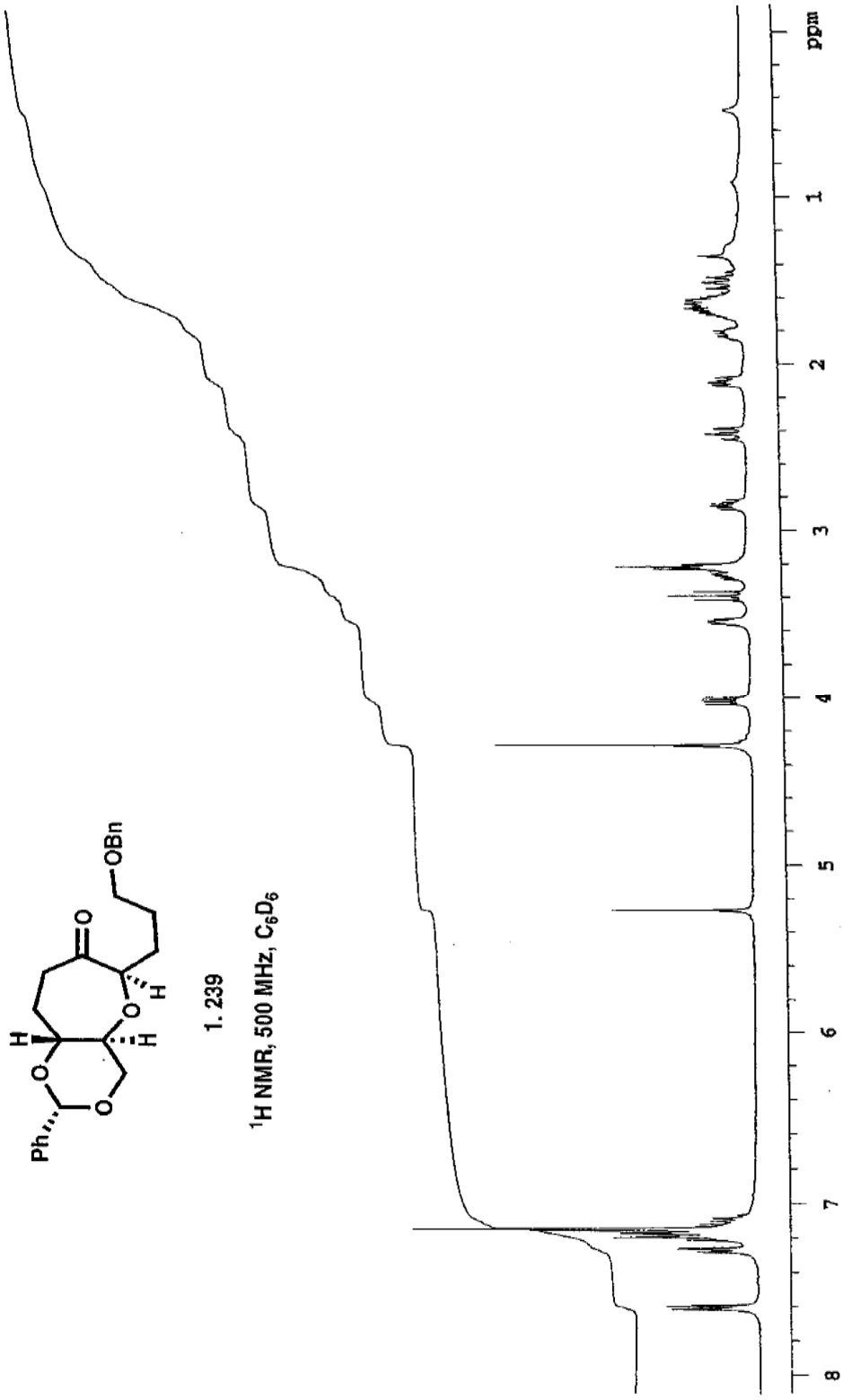

OBn
H
O
O
H
O
Ph
1. 238
^{1}H NMR, 500 MHz, C_6D_6
ppm
1
2
3
4
5
6
7
8

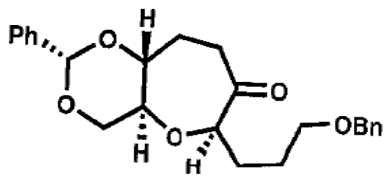


1. 238

^{13}C NMR, 125 MHz, C_6D_6

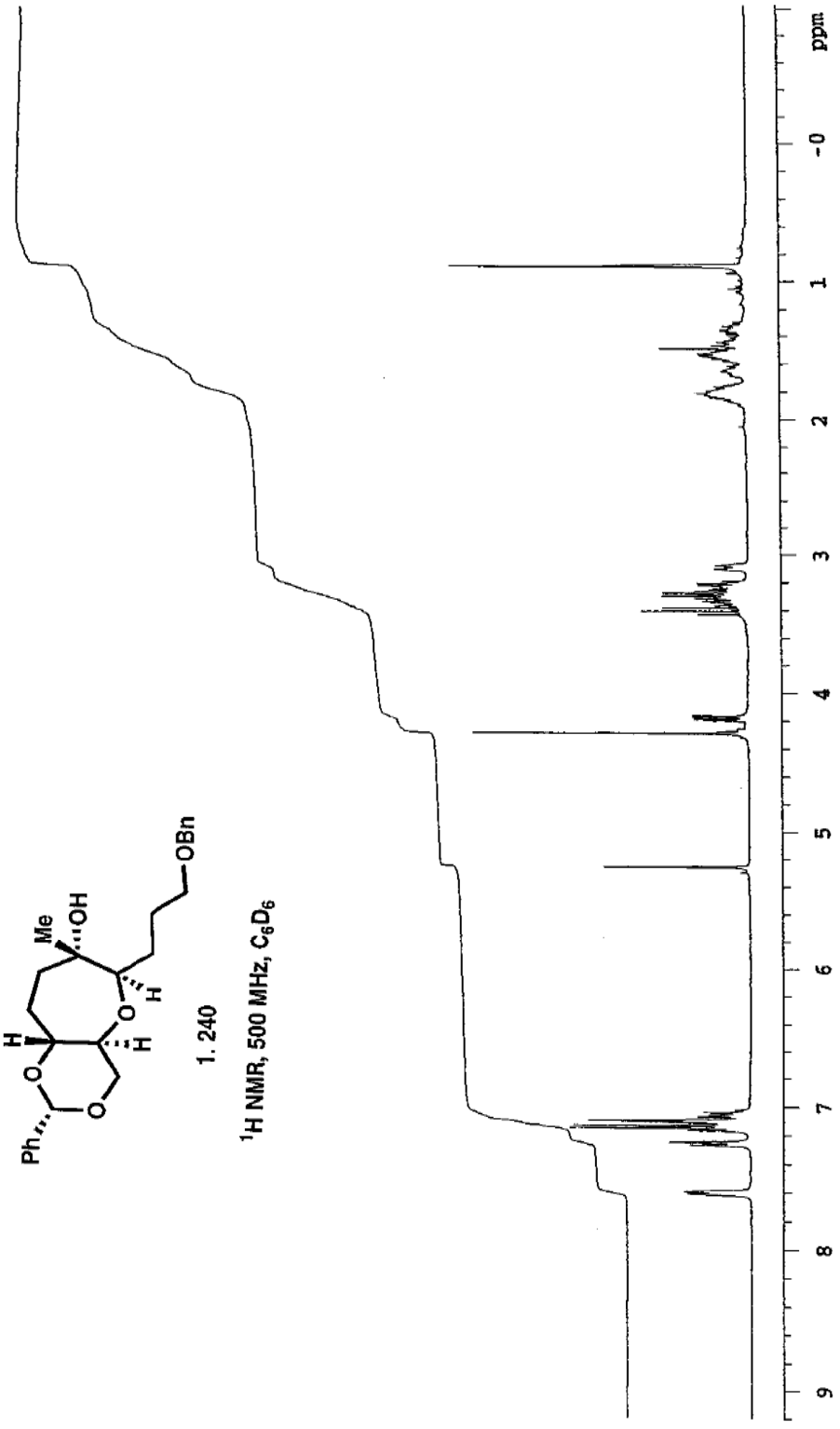


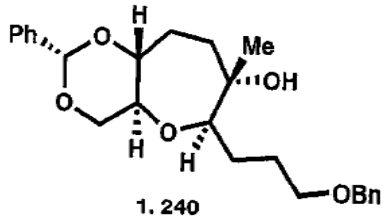

OBn
O
H
O
H
O
H
O
Ph
1. 239
^{1}H NMR, 500 MHz, C_6D_6
ppm
1
2
3
4
5
6
7
8



1. 239

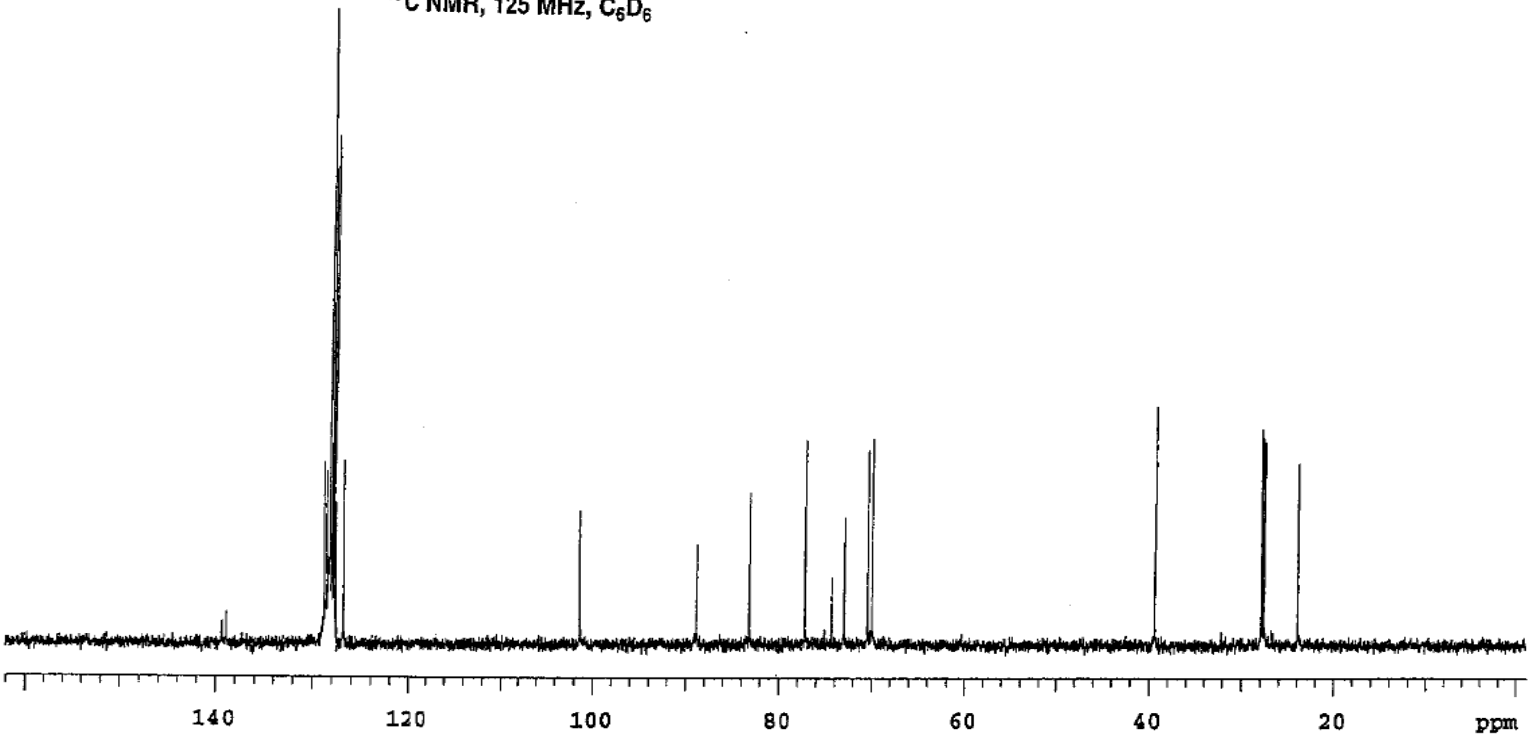
^{13}C NMR, 125 MHz, C_6D_6

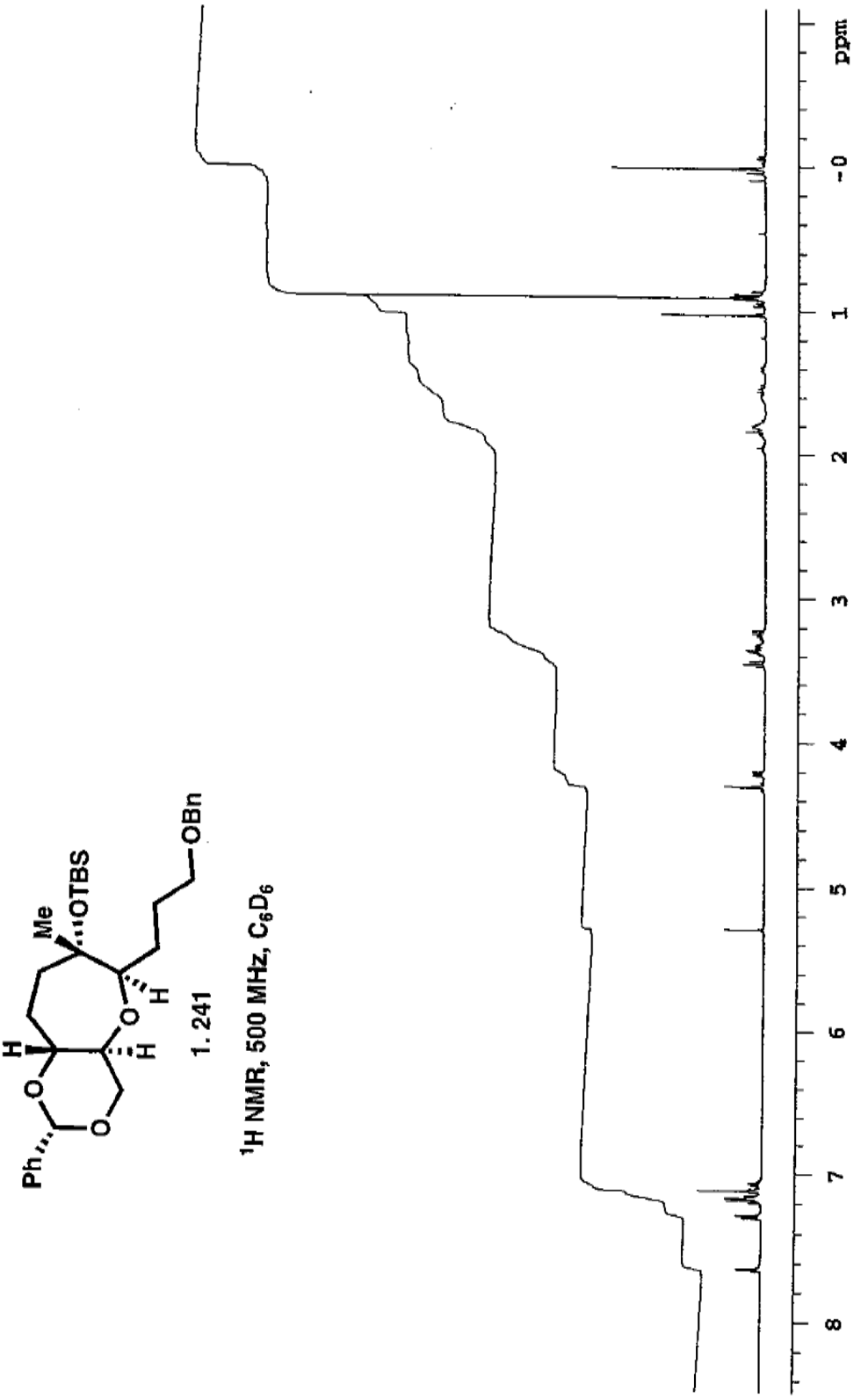

Me
OH
OBn
H
O
O
O
O
H
H
Ph
1. 240
^{1}H NMR, 500 MHz, C_6D_6
ppm
9
8
7
6
5
4
3
2
1
-0

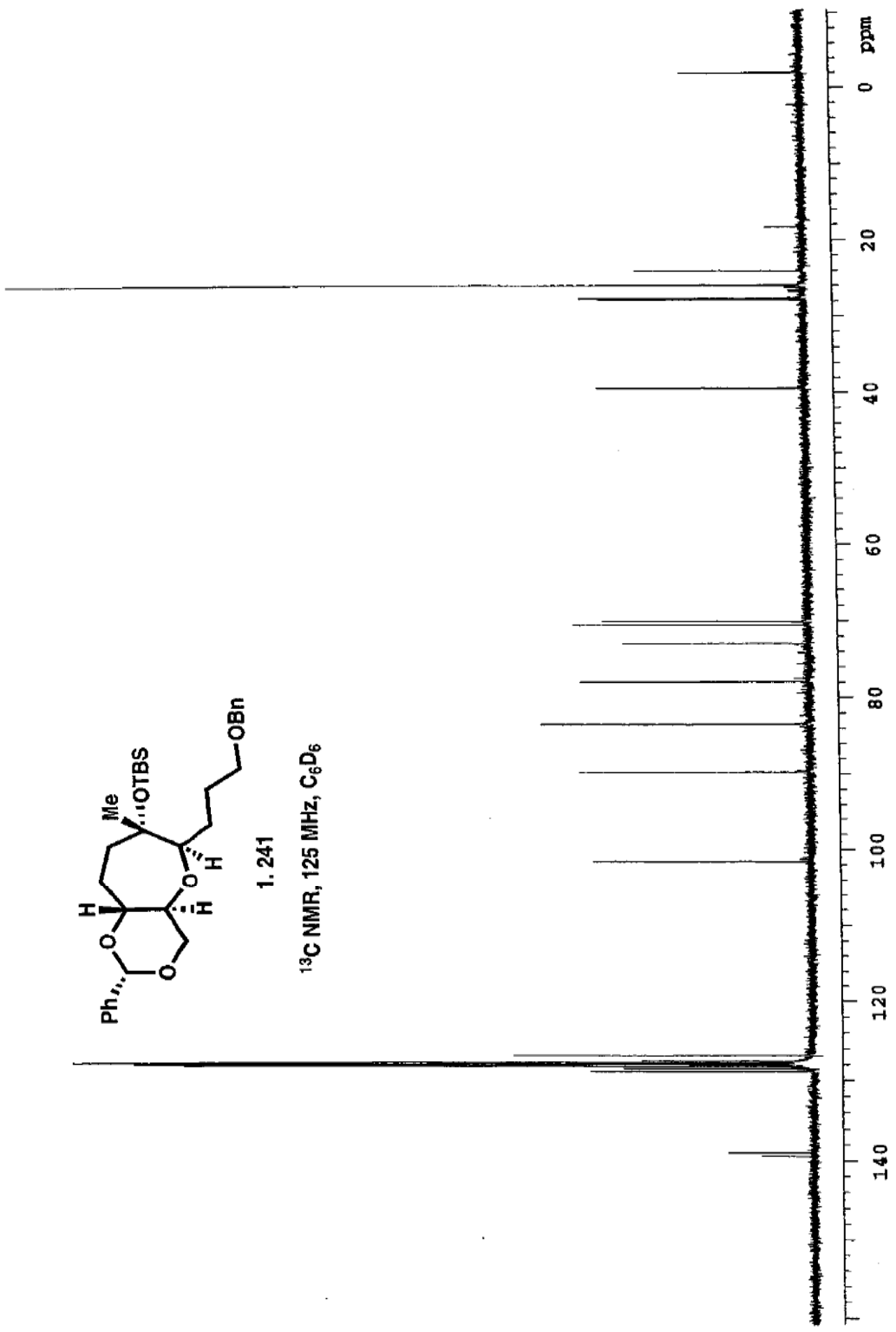


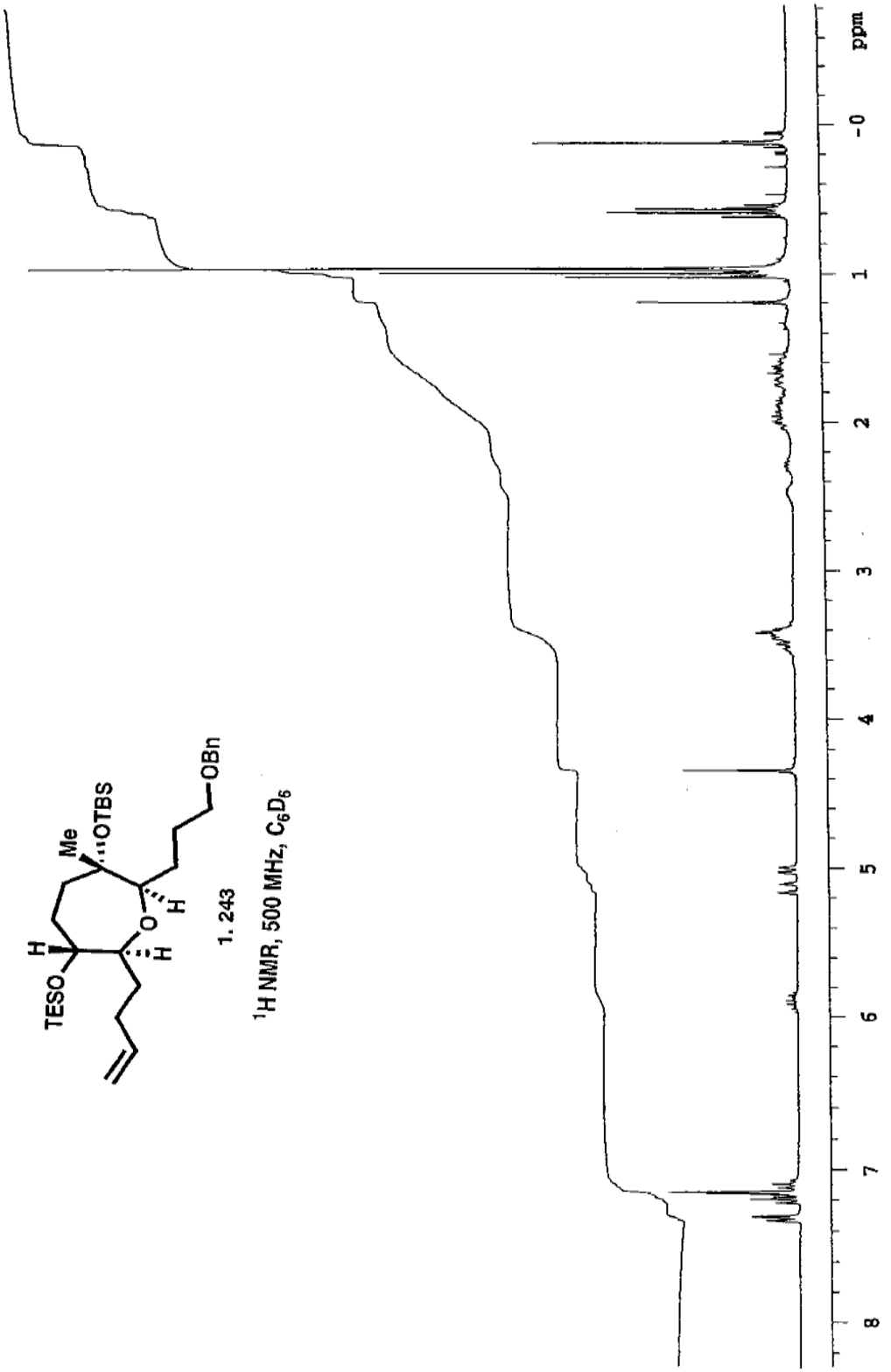
1. 240

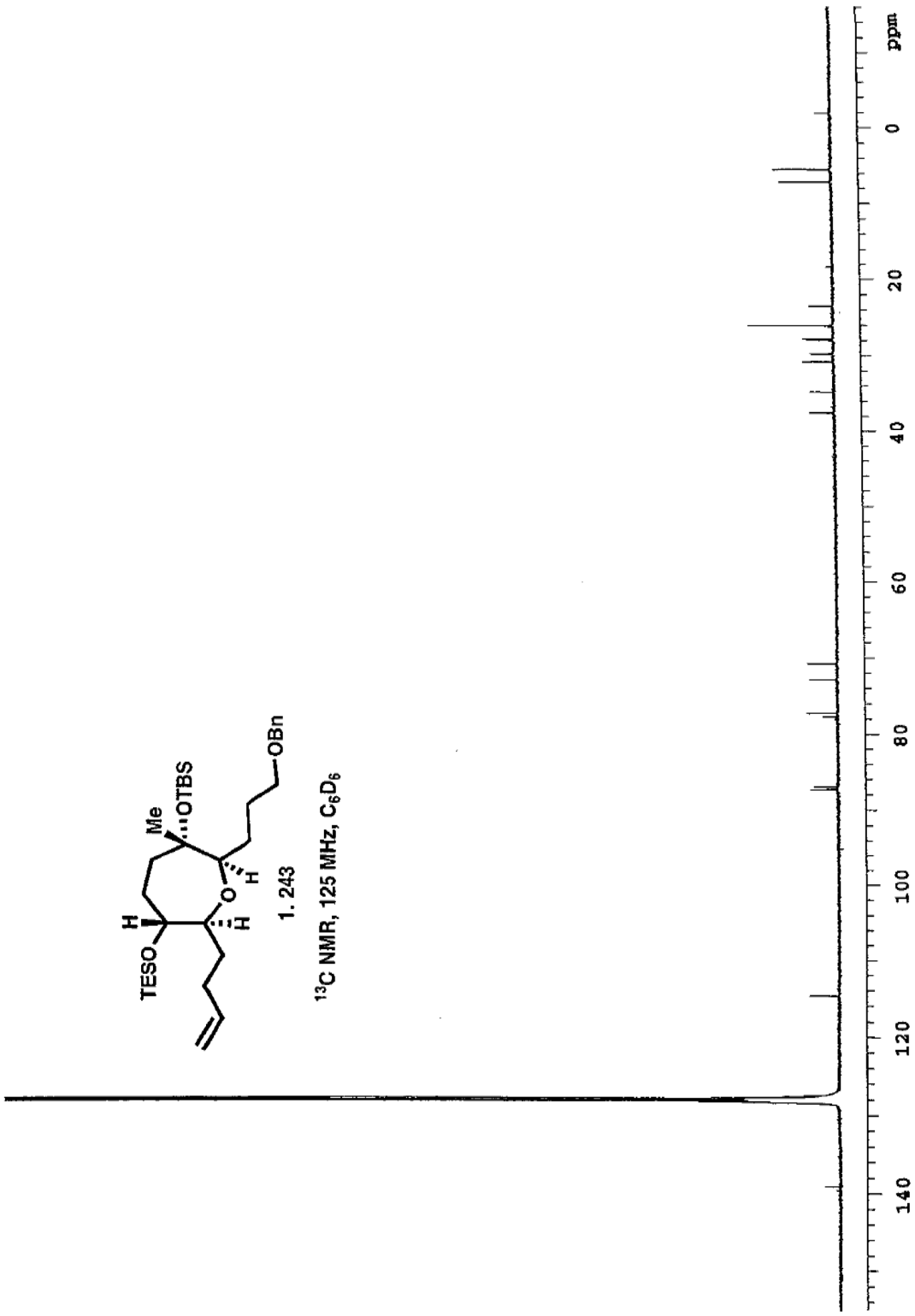
^{13}C NMR, 125 MHz, C_6D_6

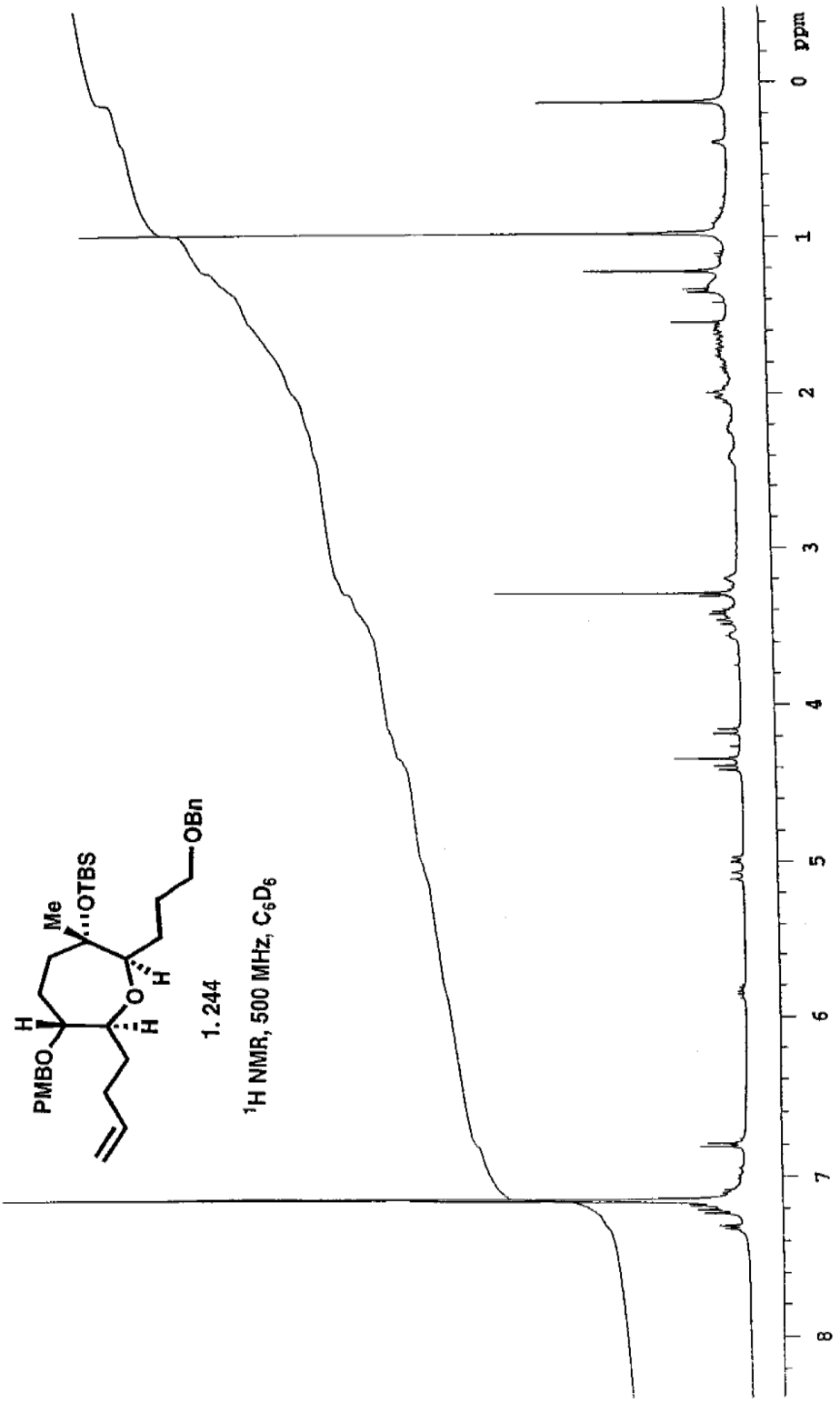


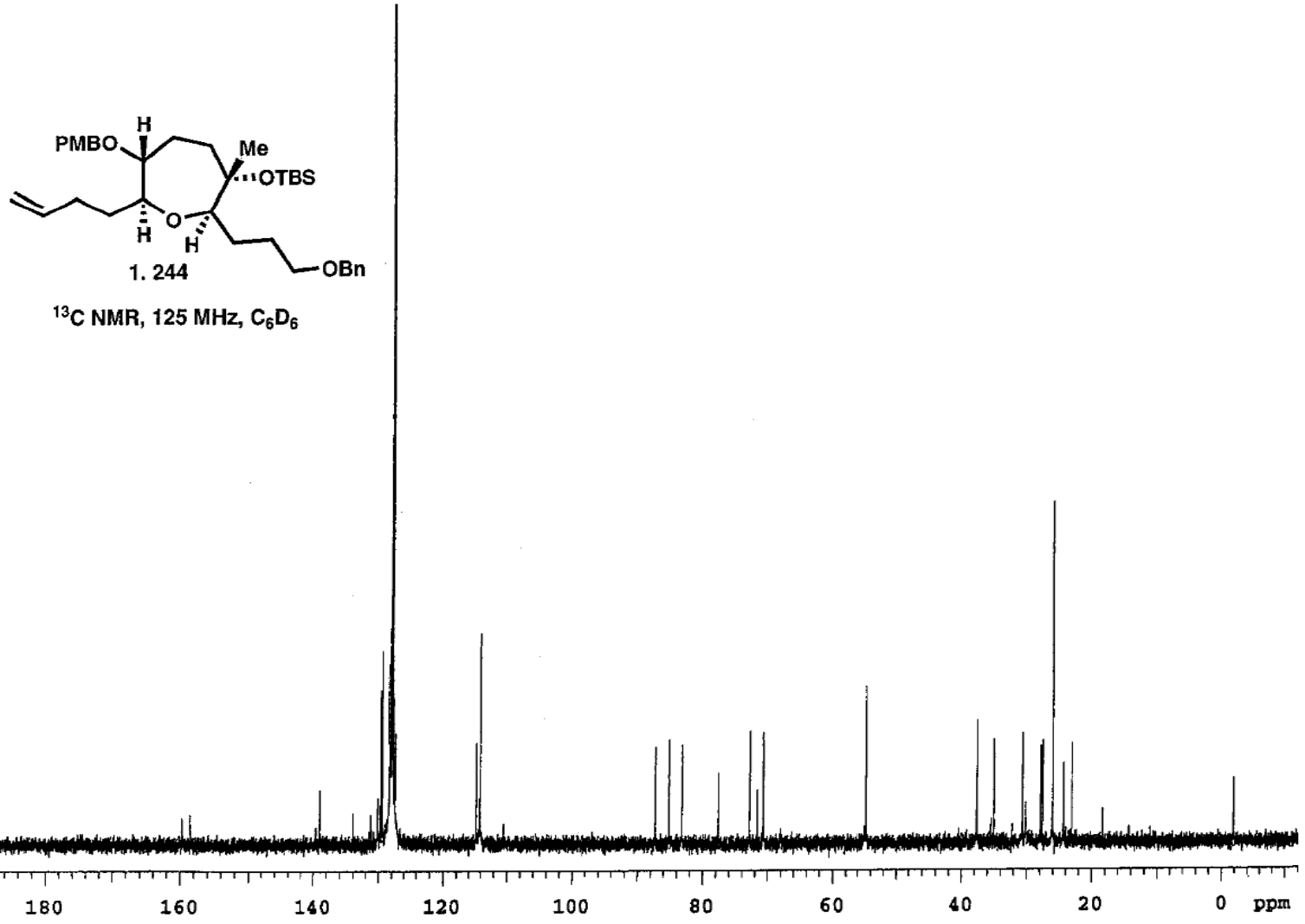

Ph
O
O
H
O
H
Me
OTBS
OBn
1.241
^{1}H NMR, 500 MHz, C_6D_6
8
7
6
5
4
3
2
1
-0
ppm


OBn
Me
OTBS
H
O
O
H
O
Ph
1. 241
^{13}C NMR, 125 MHz, C_6D_6
ppm
0
20
40
60
80
100
120
140


TESO
H
Me
OTBS
O
H
H
OBn
1. 243
^{1}H NMR, 500 MHz, C_6D_6
ppm
8
7
6
5
4
3
2
1
-0

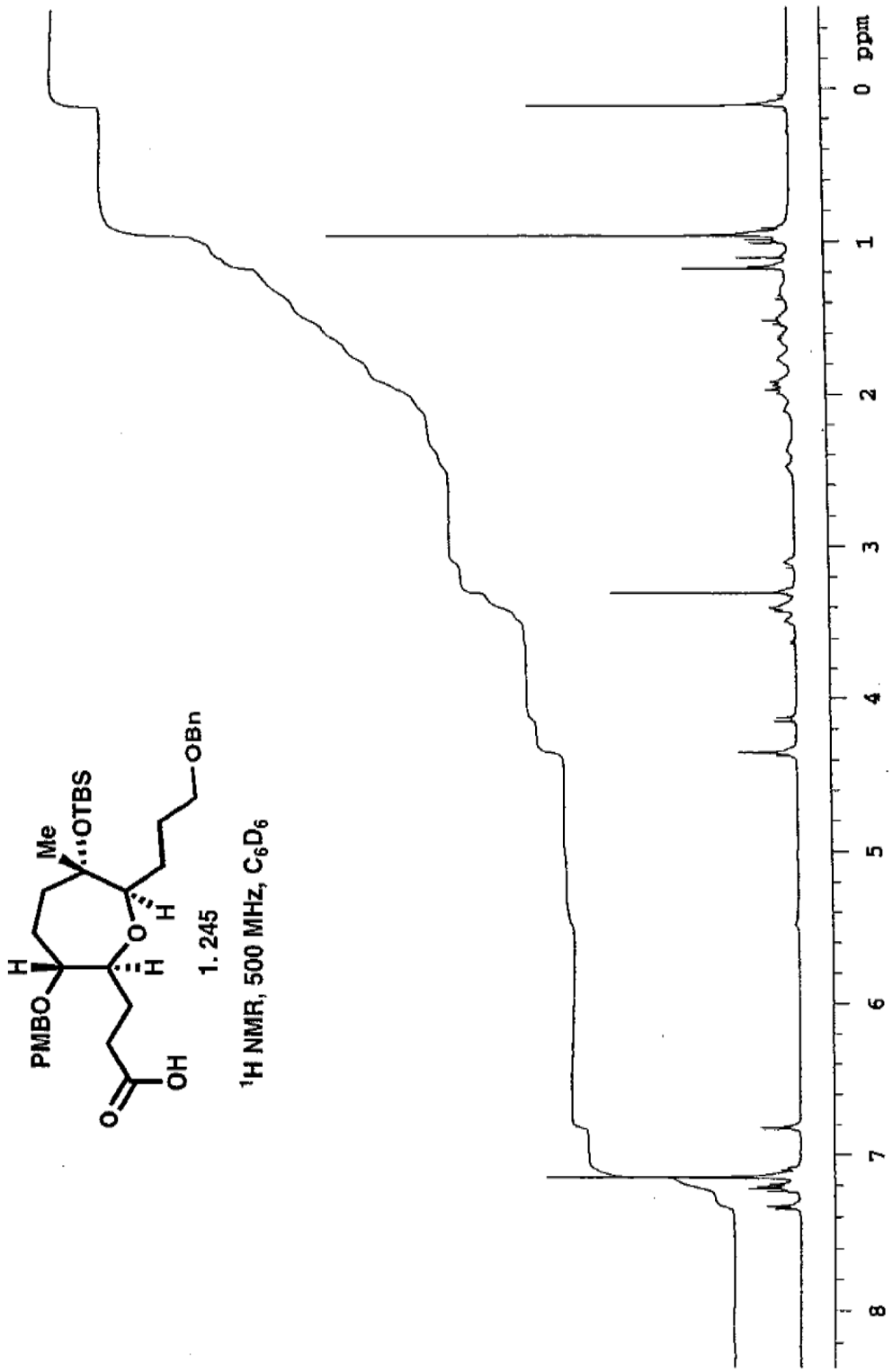

TESO
H
Me
OTBS
O
H
OBn
1. 243
^{13}C NMR, 125 MHz, C_6D_6
ppm
0
20
40
60
80
100
120
140

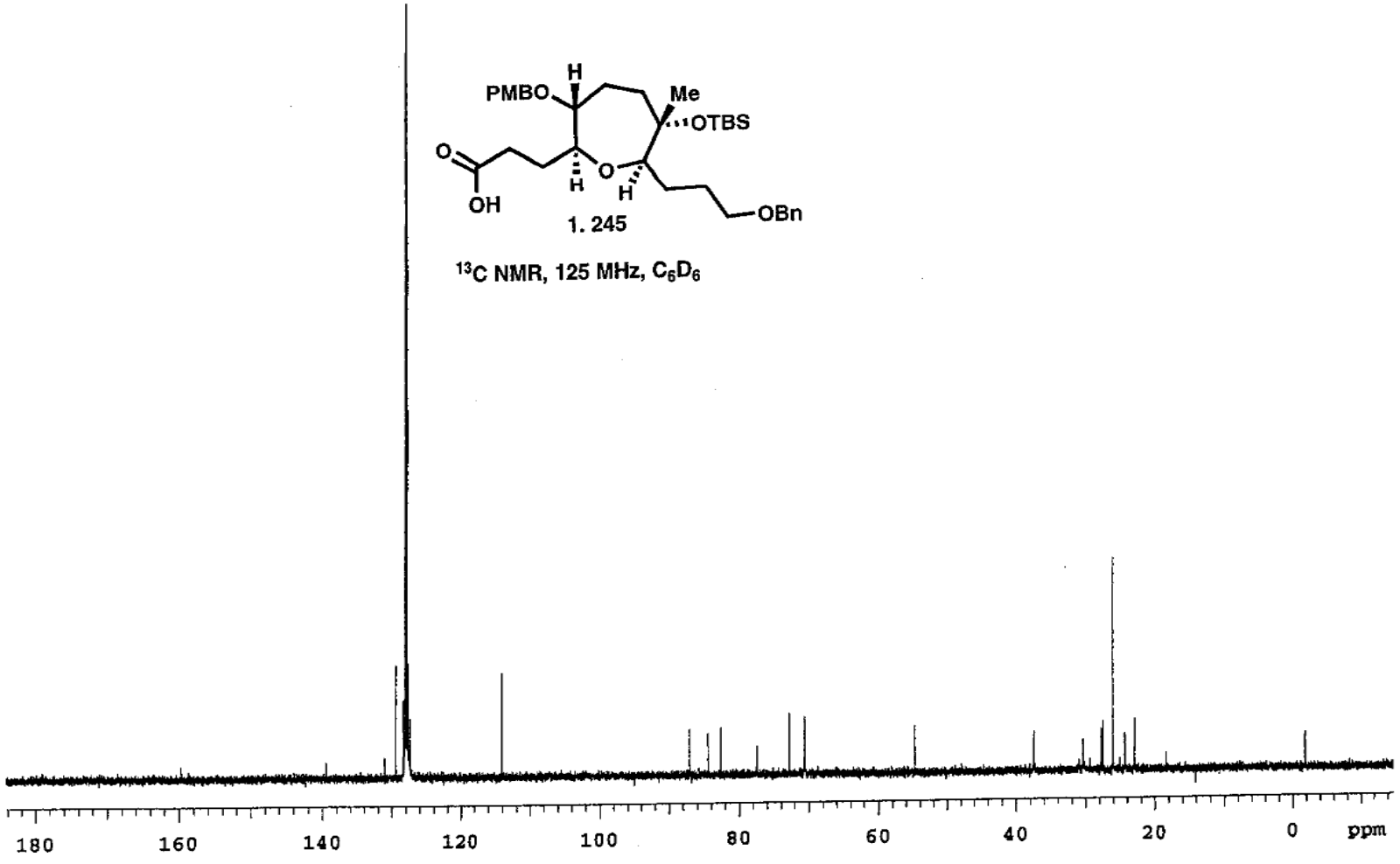

PMBO
H
Me
OTBS
O
H
OBn
1. 244
^{1}H NMR, 500 MHz, C_6D_6
8
7
6
5
4
3
2
1
0 ppm

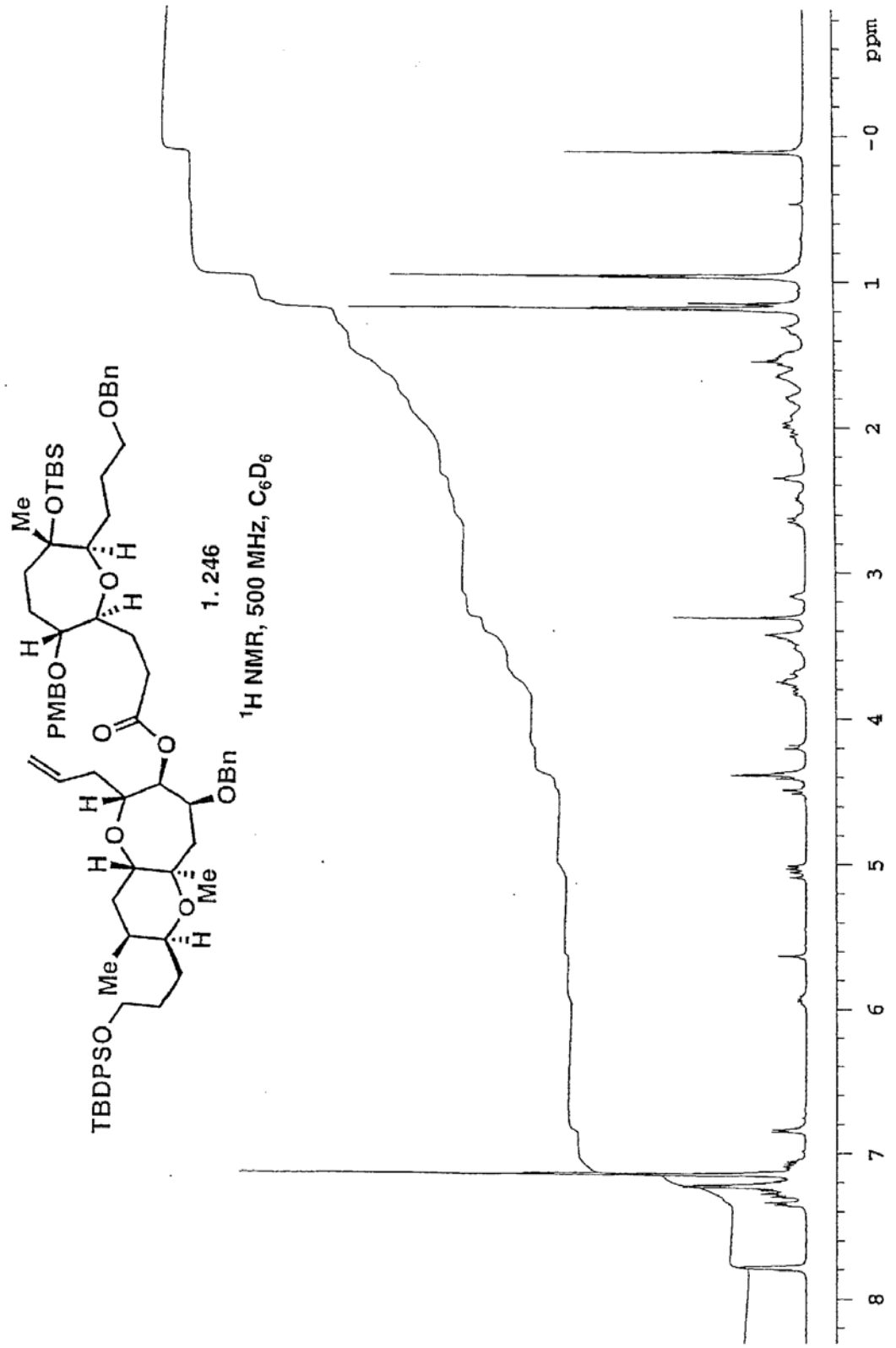


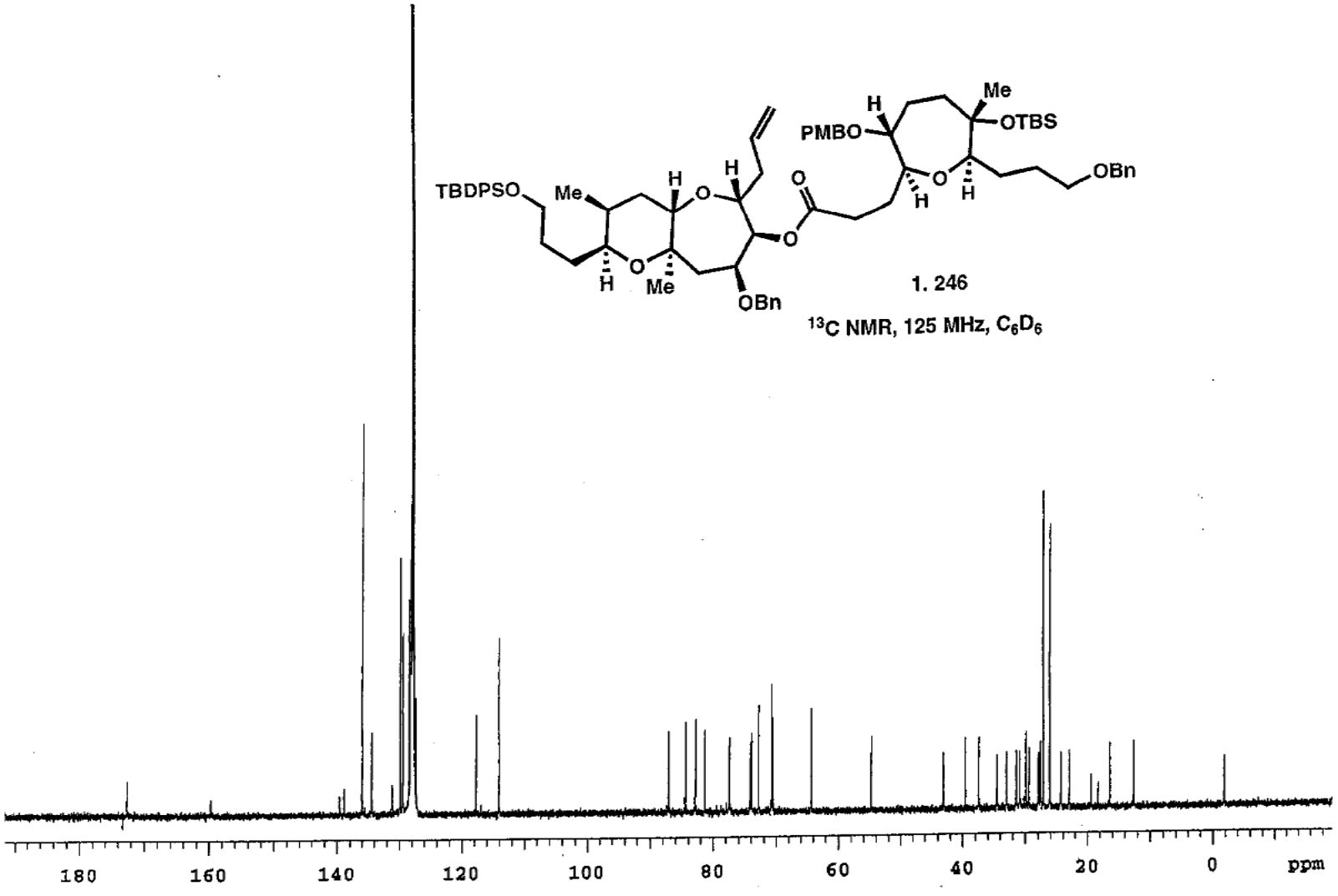
1. 244

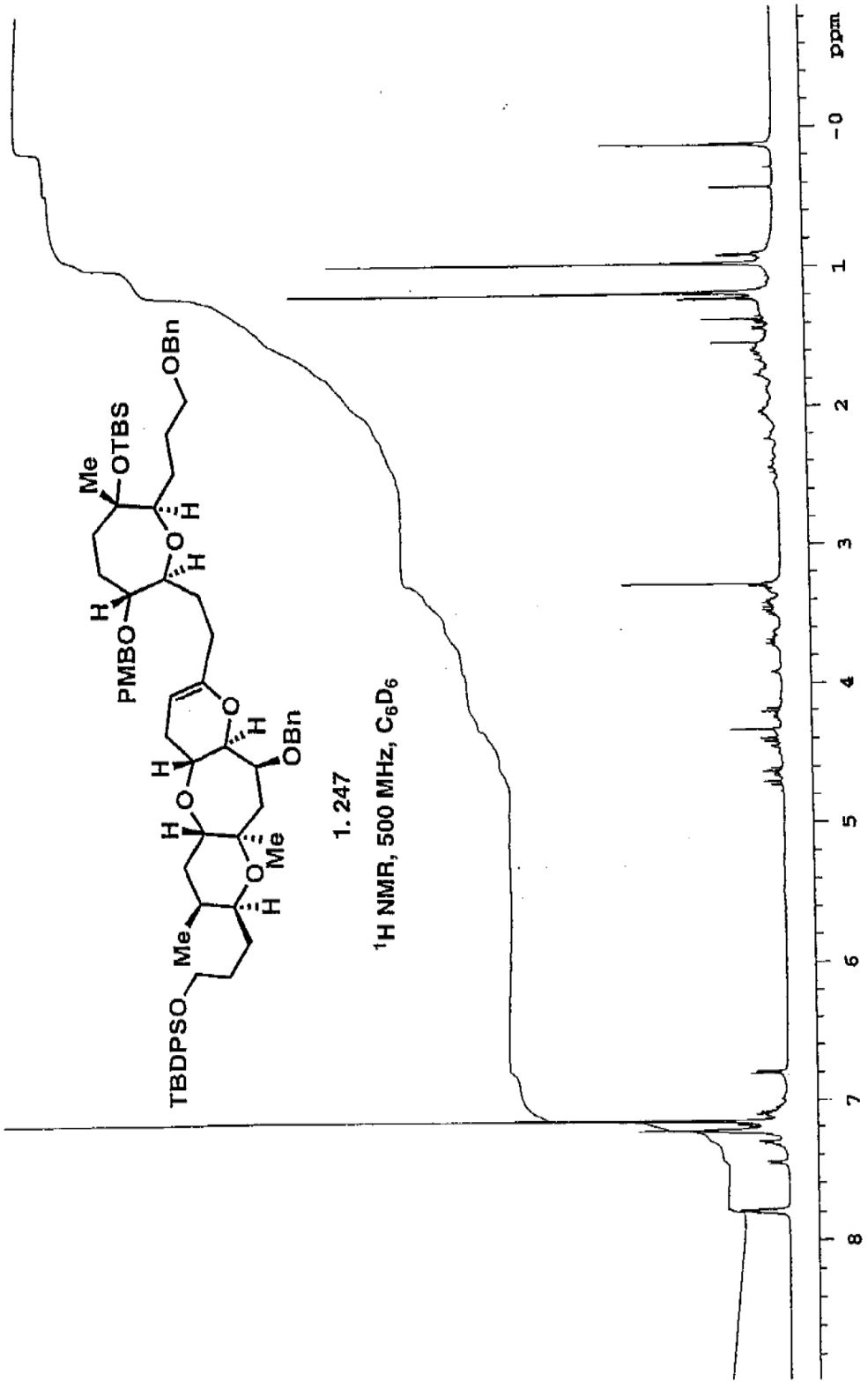
^{13}C NMR, 125 MHz, C_6D_6

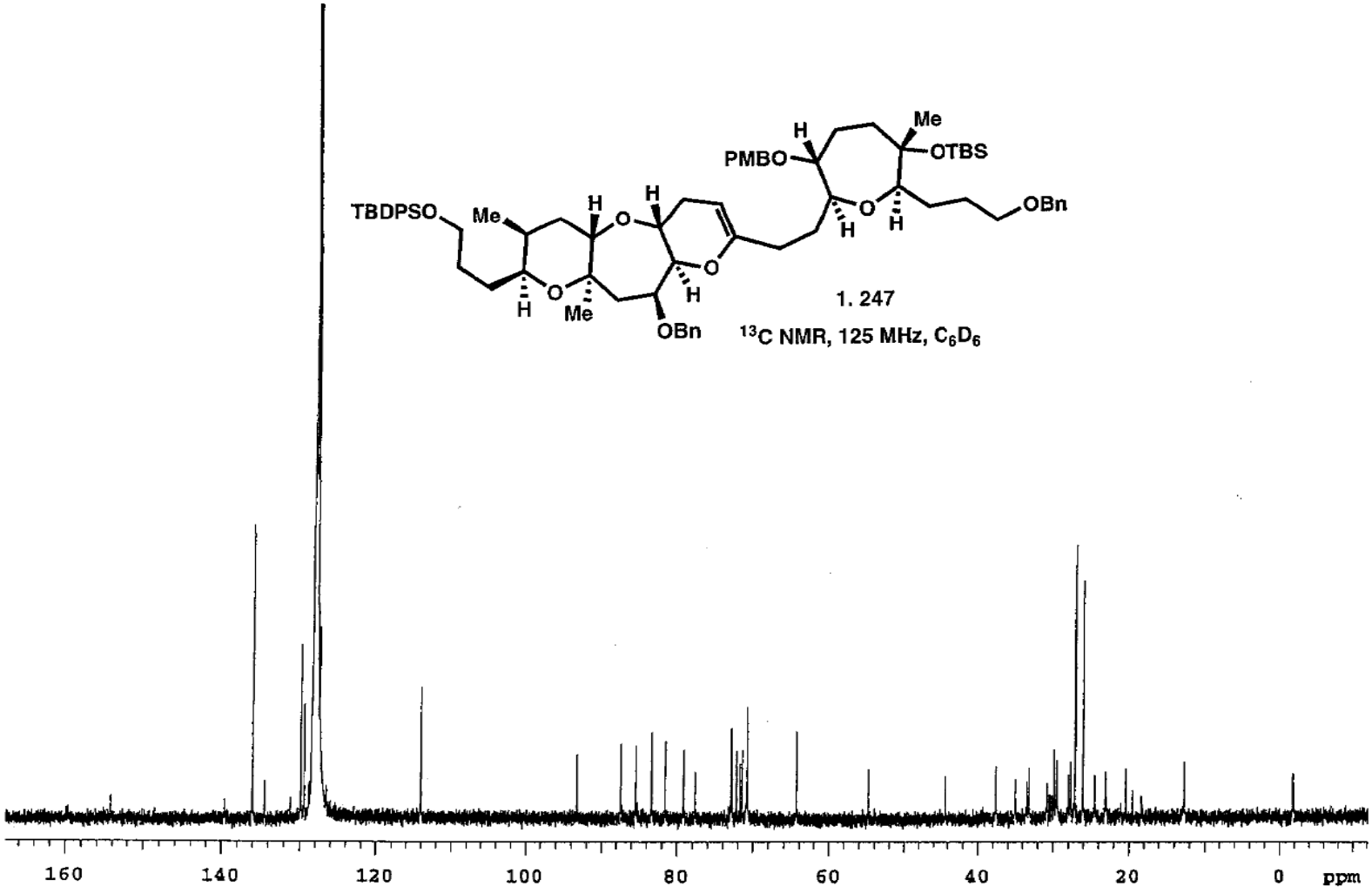

PMBO
H
Me
OTBS
O
H
H
OBn
OH
O
1. 245
^{1}H NMR, 500 MHz, C_6D_6
8
7
6
5
4
3
2
1
0 ppm

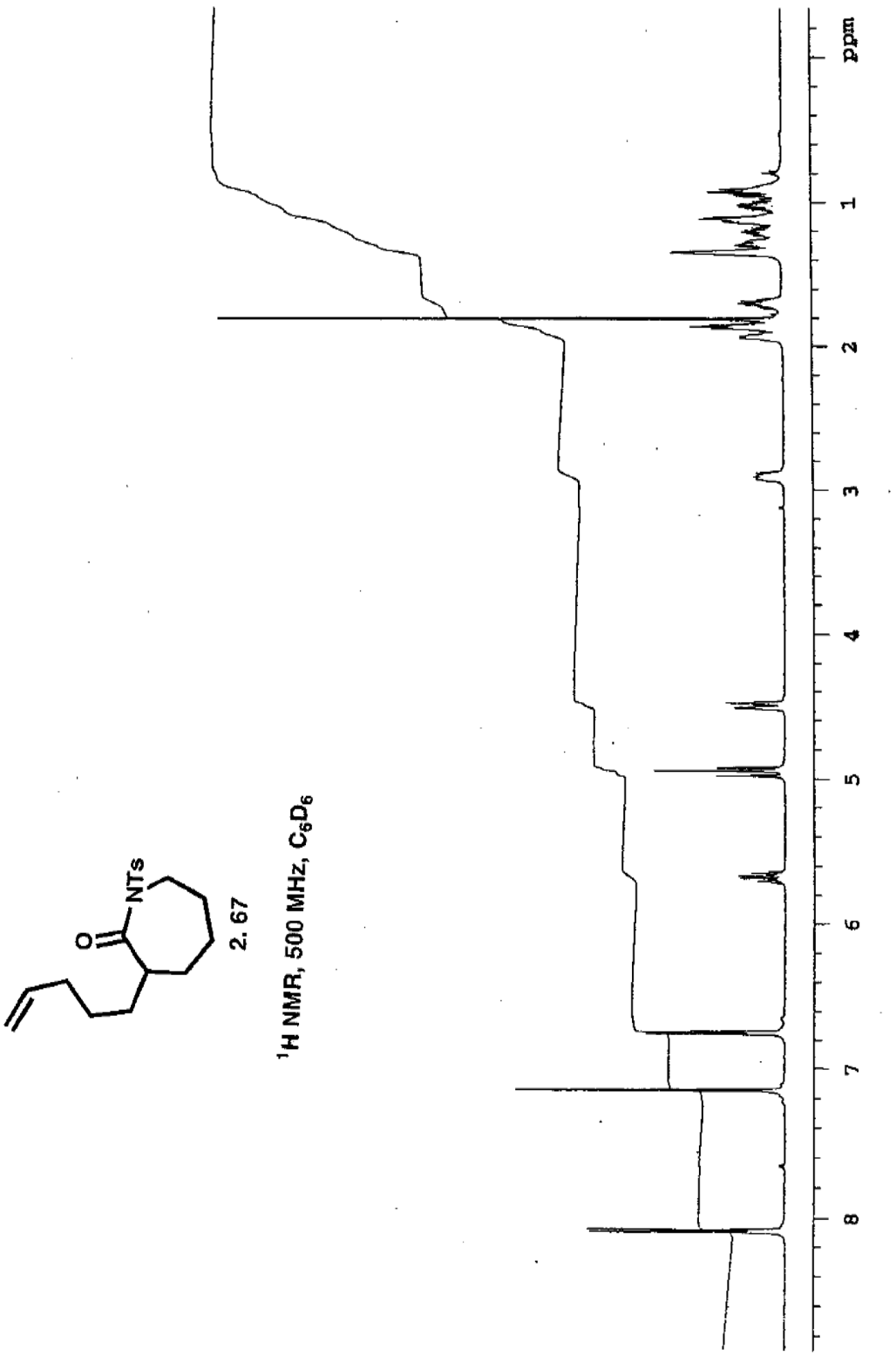

PMBO
H
Me
OTBS
O
OH
O
H
H
OBn
1. 245
^{13}C NMR, 125 MHz, C_6D_6
180
160
140
120
100
80
60
40
20
0
ppm

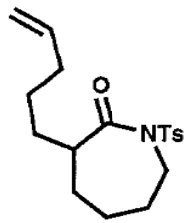

TBDPSO
Me
OTBS
PMBO
OBn
OBn
Me
1.246
^{1}H NMR, 500 MHz, C_6D_6
ppm
8
7
6
5
4
3
2
1
0


TBDPSO
Me
H
H
O
O
O
H
Me
OBn
PMBO
H
Me
OTBS
O
H
H
OBn
1. 246
^{13}C NMR, 125 MHz, C_6D_6
180
160
140
120
100
80
60
40
20
0
ppm


TBDPSO
Me
PMBO
H
Me
OTBS
OBn
H
O
H
O
H
H
O
H
O
H
Me
O
H
OBn
1. 247
^{1}H NMR, 500 MHz, C_6D_6
ppm
-0
1
2
3
4
5
6
7
8

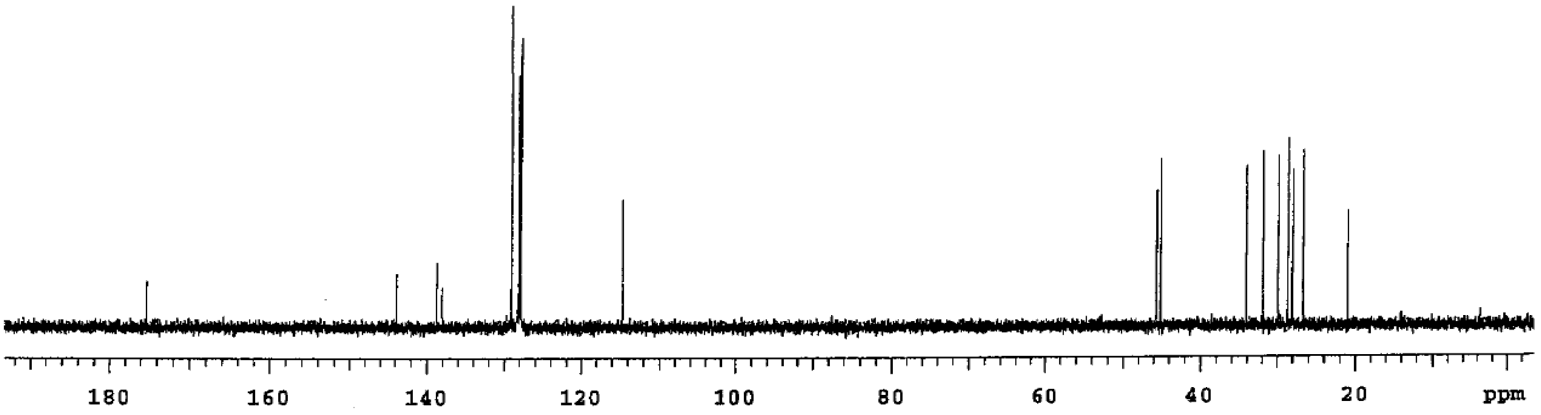

TBDPSO
Me
H
O
H
O
H
O
Me
H
Me
OBn
PMBO
H
Me
OTBS
O
H
H
OBn
1. 247
^{13}C NMR, 125 MHz, C_6D_6
160
140
120
100
80
60
40
20
0
ppm

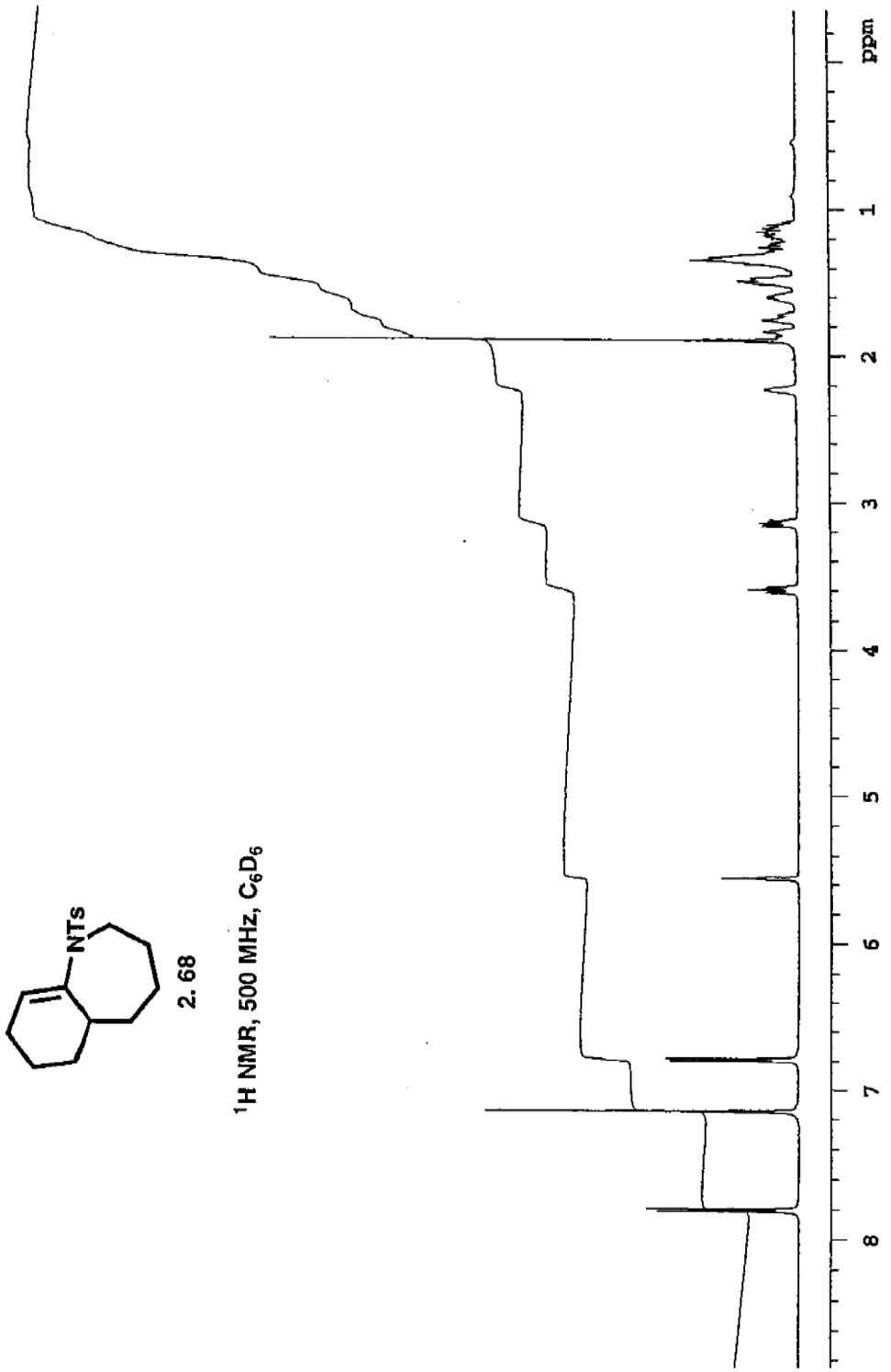

NTs
O
2. 67
^{1}H NMR, 500 MHz, C_6D_6
ppm
1
2
3
4
5
6
7
8

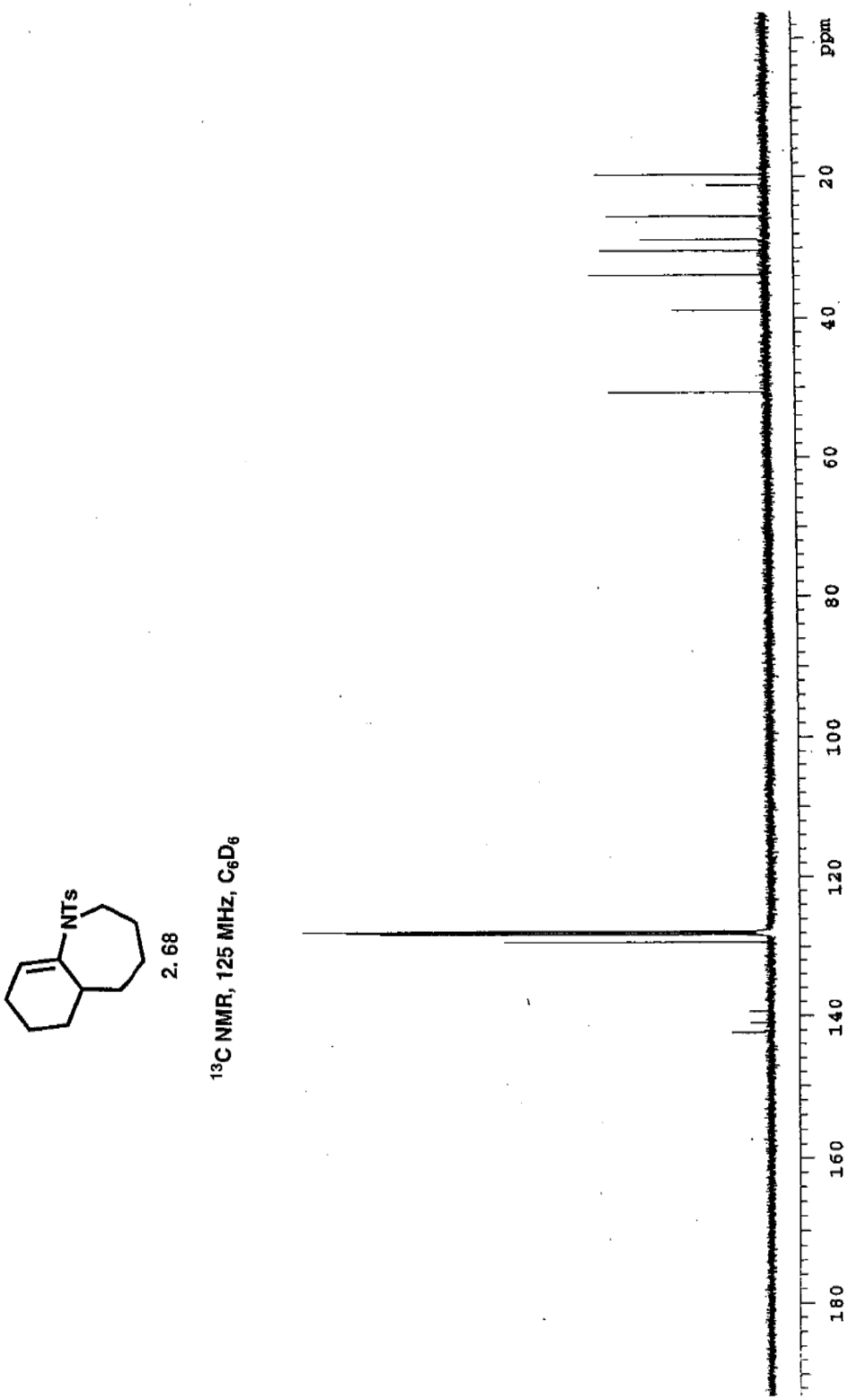


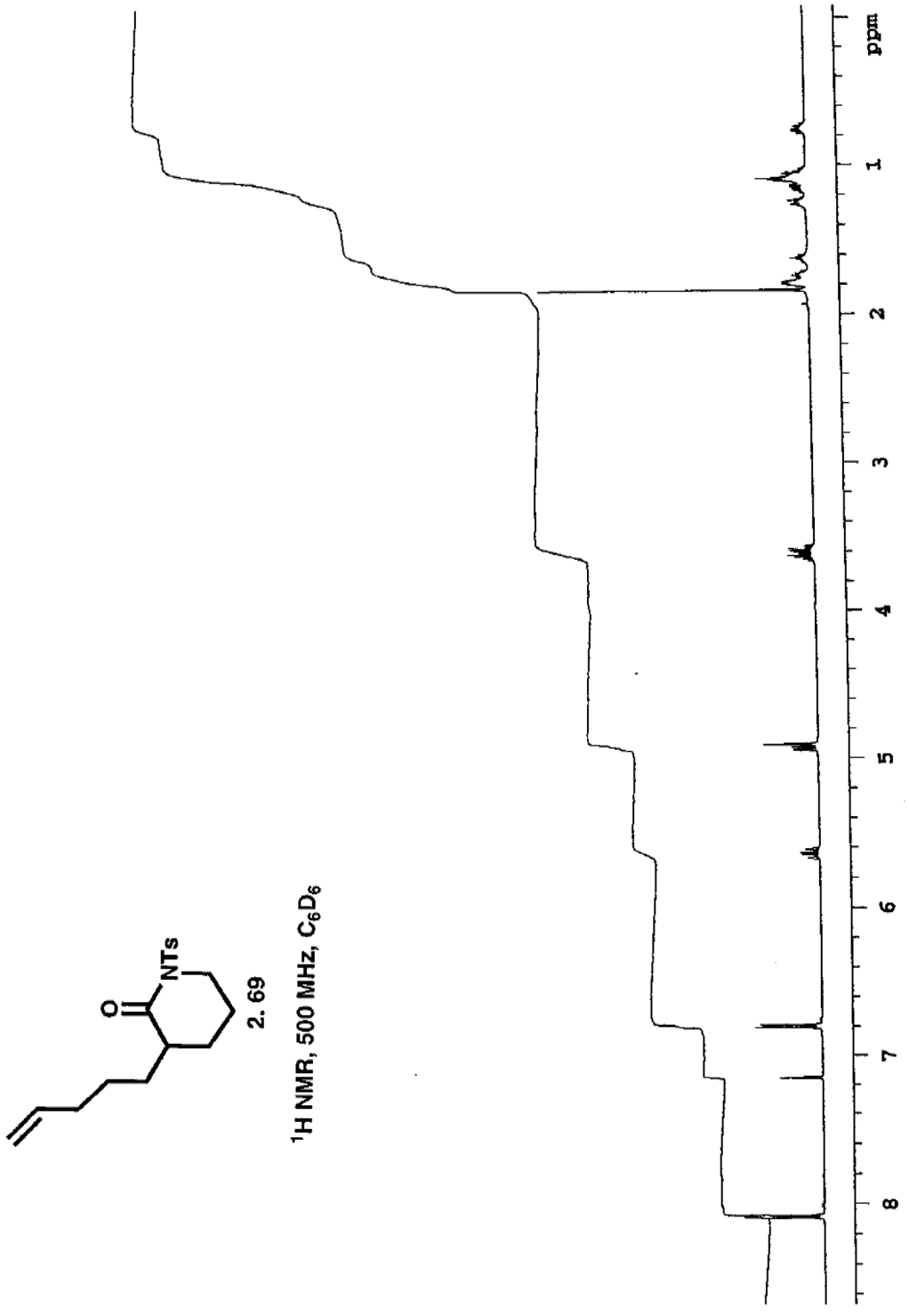
2. 67

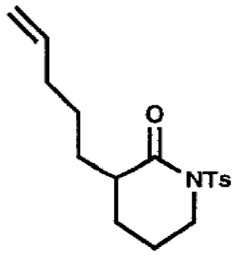
^{13}C NMR, 125 MHz, C_6D_6




NTs
2. 68
^{1}H NMR, 500 MHz, C_6D_6
ppm
1
2
3
4
5
6
7
8

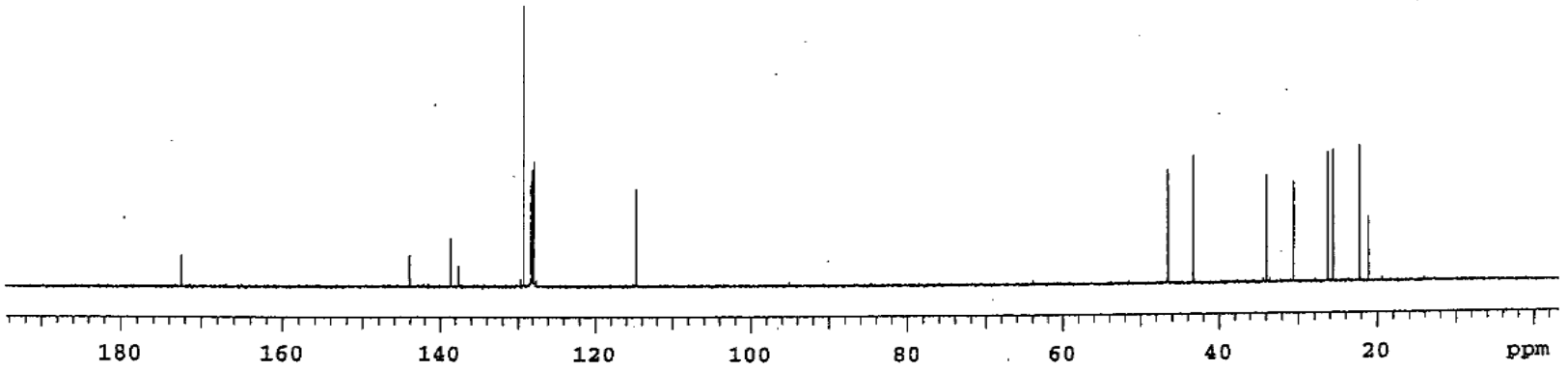

NTs
2. 68
^{13}C NMR, 125 MHz, C_6D_6
ppm
20
40
60
80
100
120
140
160
180

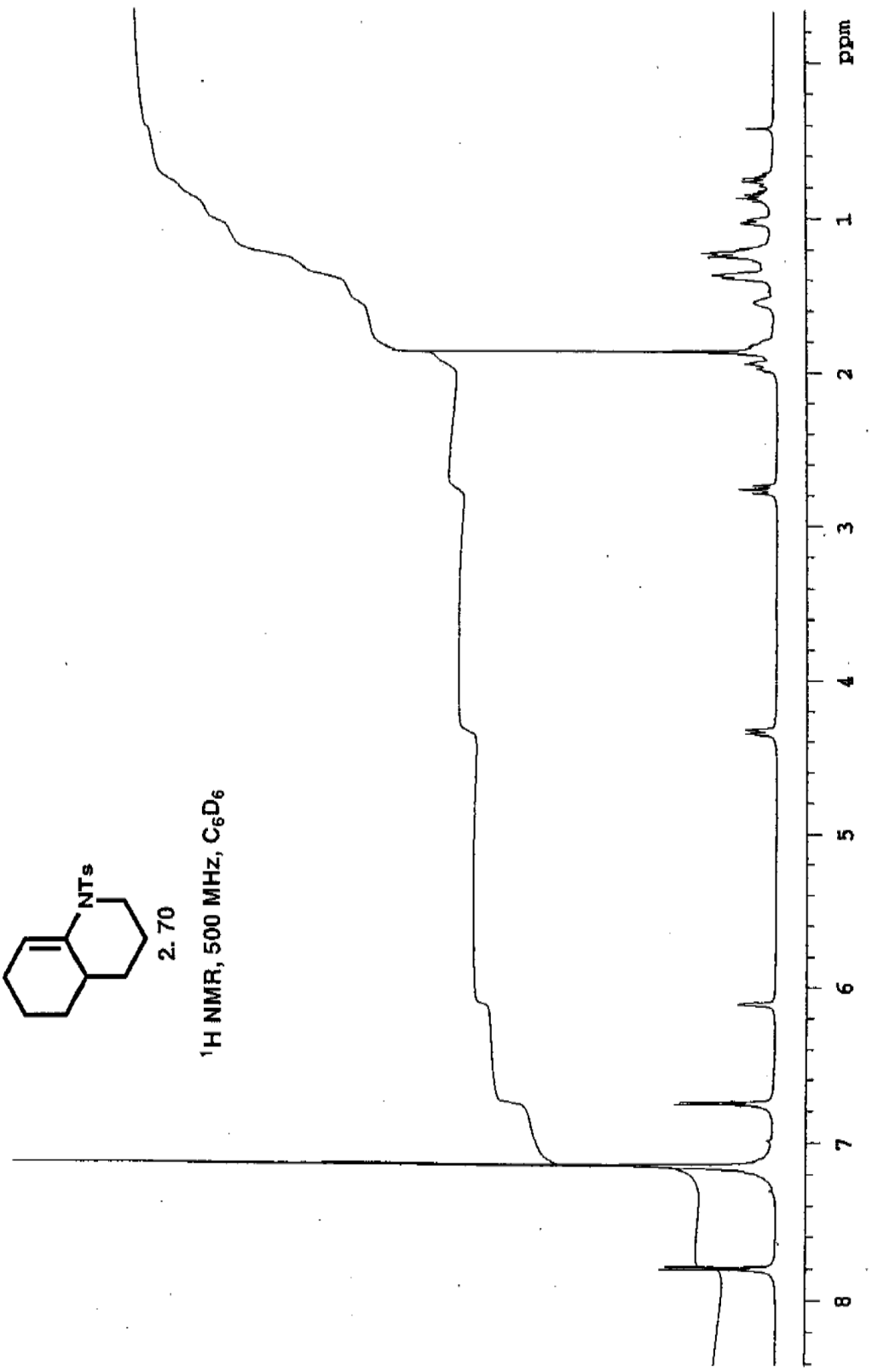

NTs
O
2. 69
^{1}H NMR, 500 MHz, C_6D_6
ppm
1
2
3
4
5
6
7
8

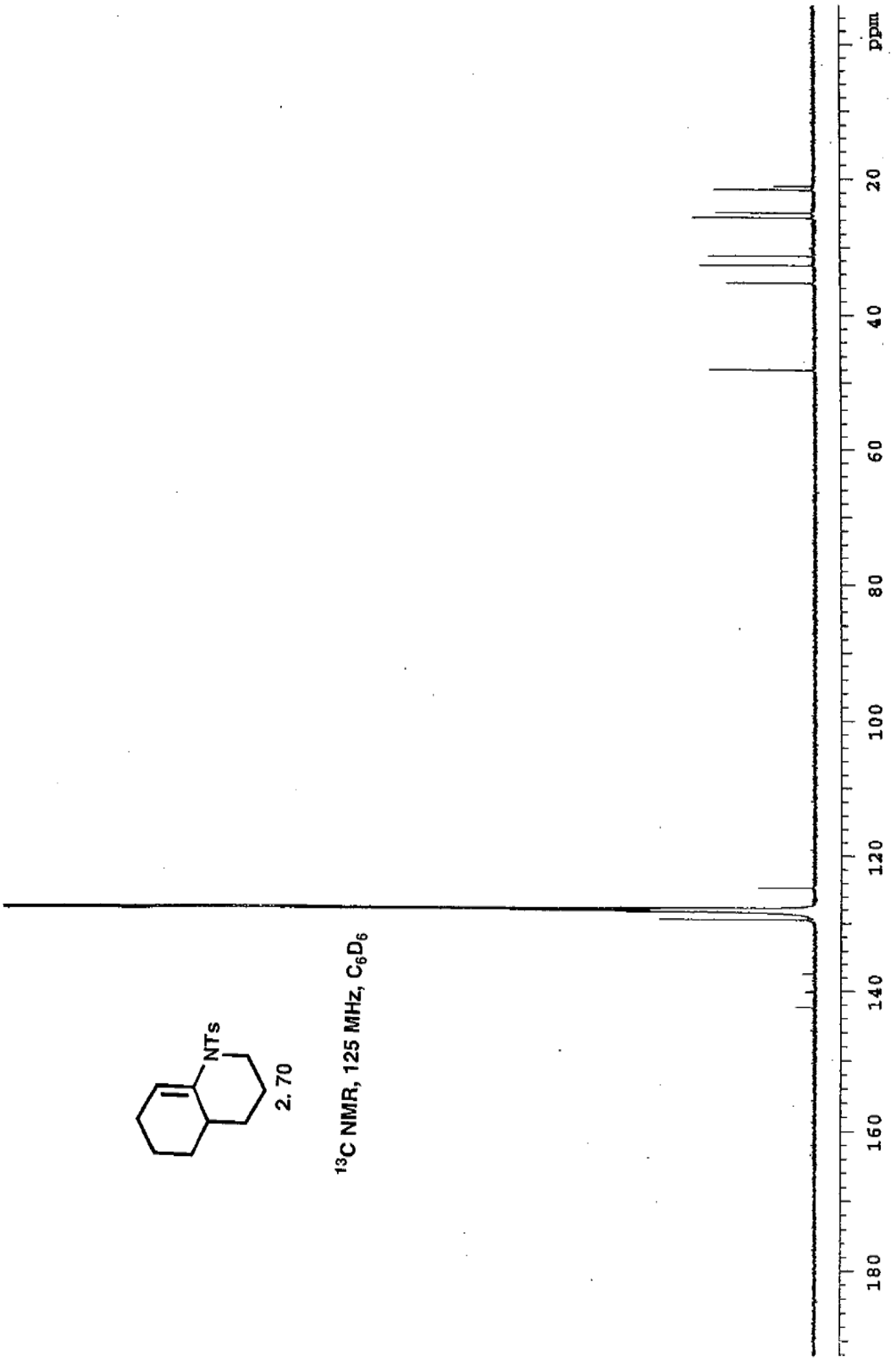


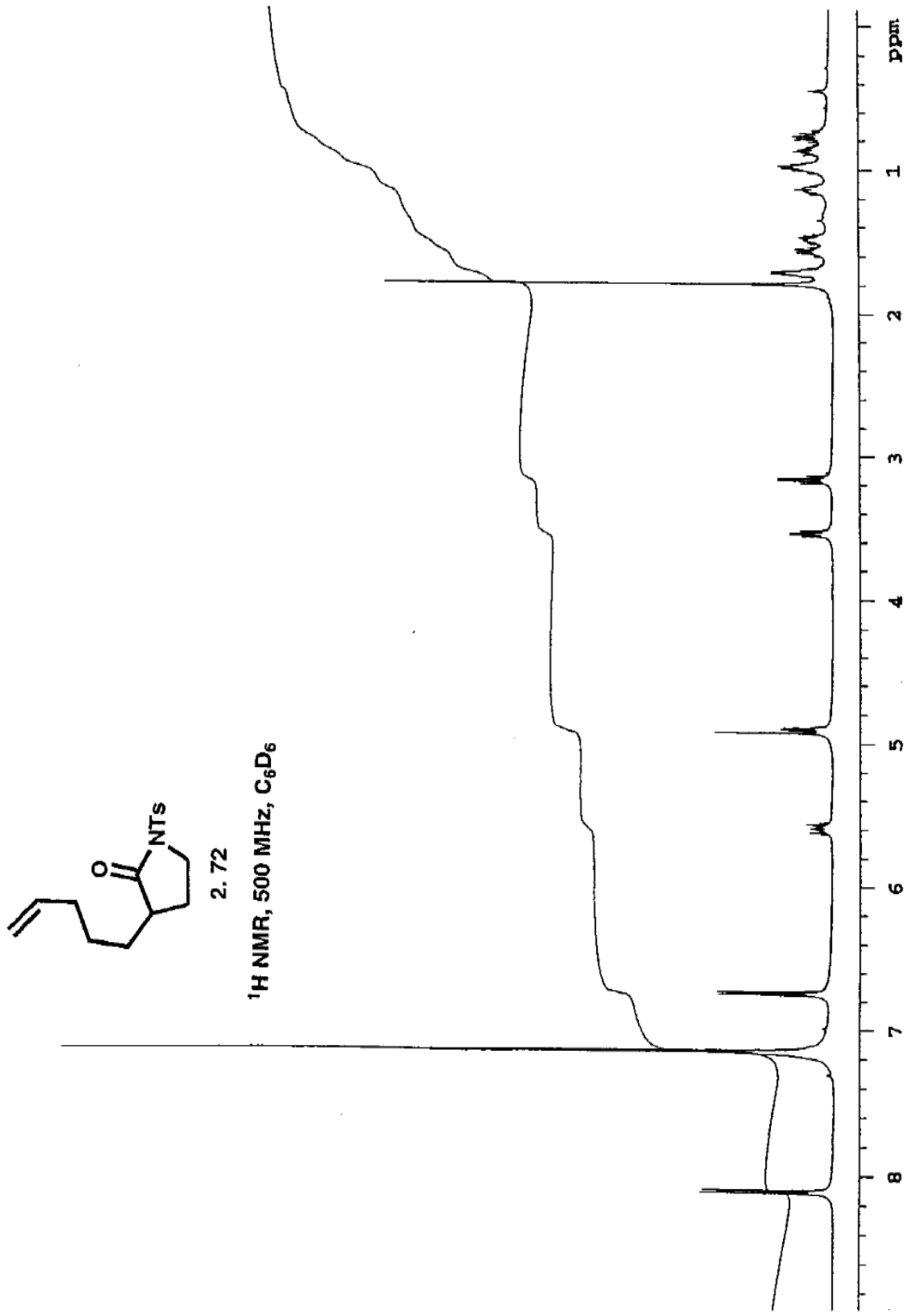
2. 69

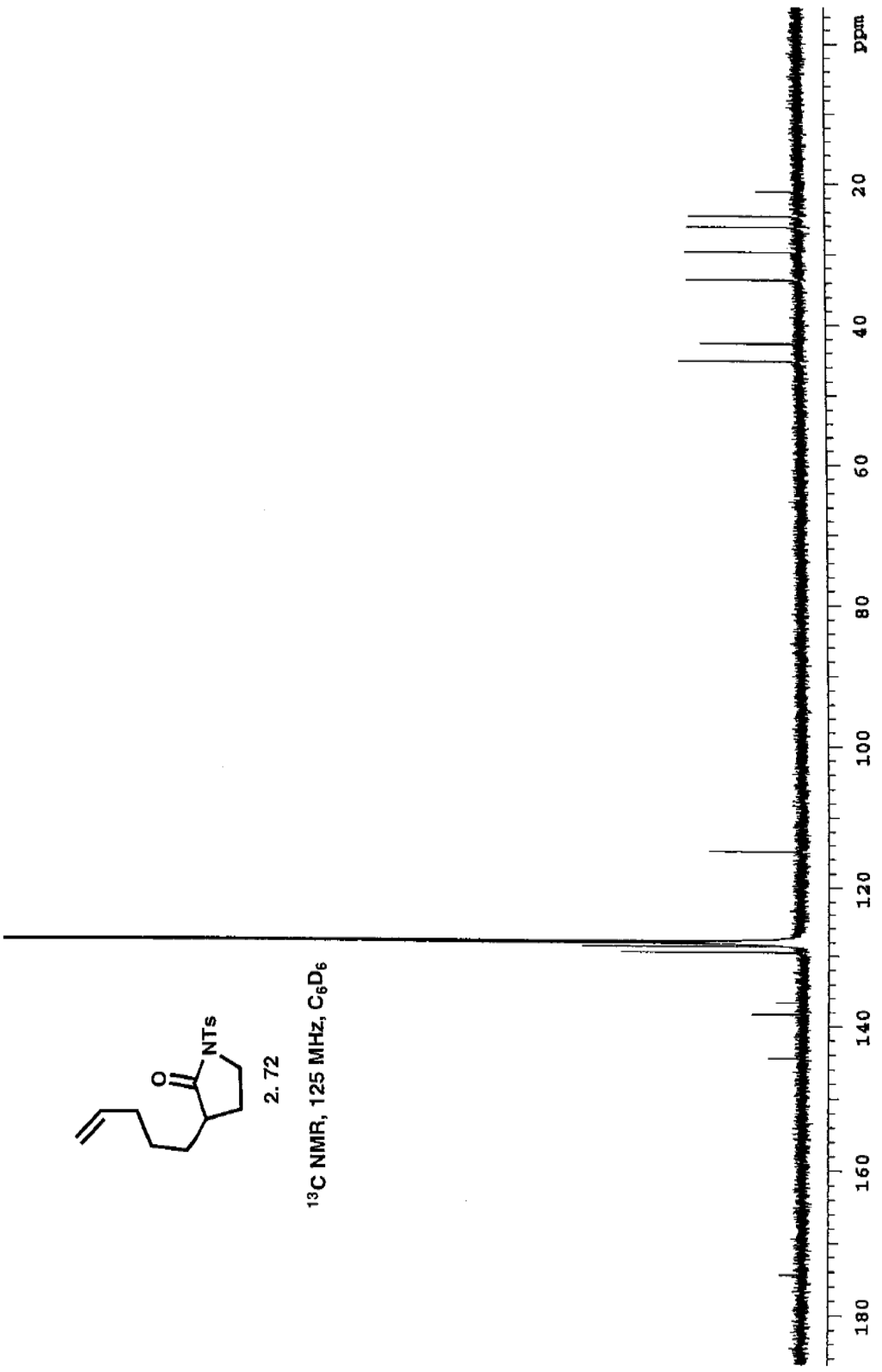
^{13}C NMR, 125 MHz, C_6D_6

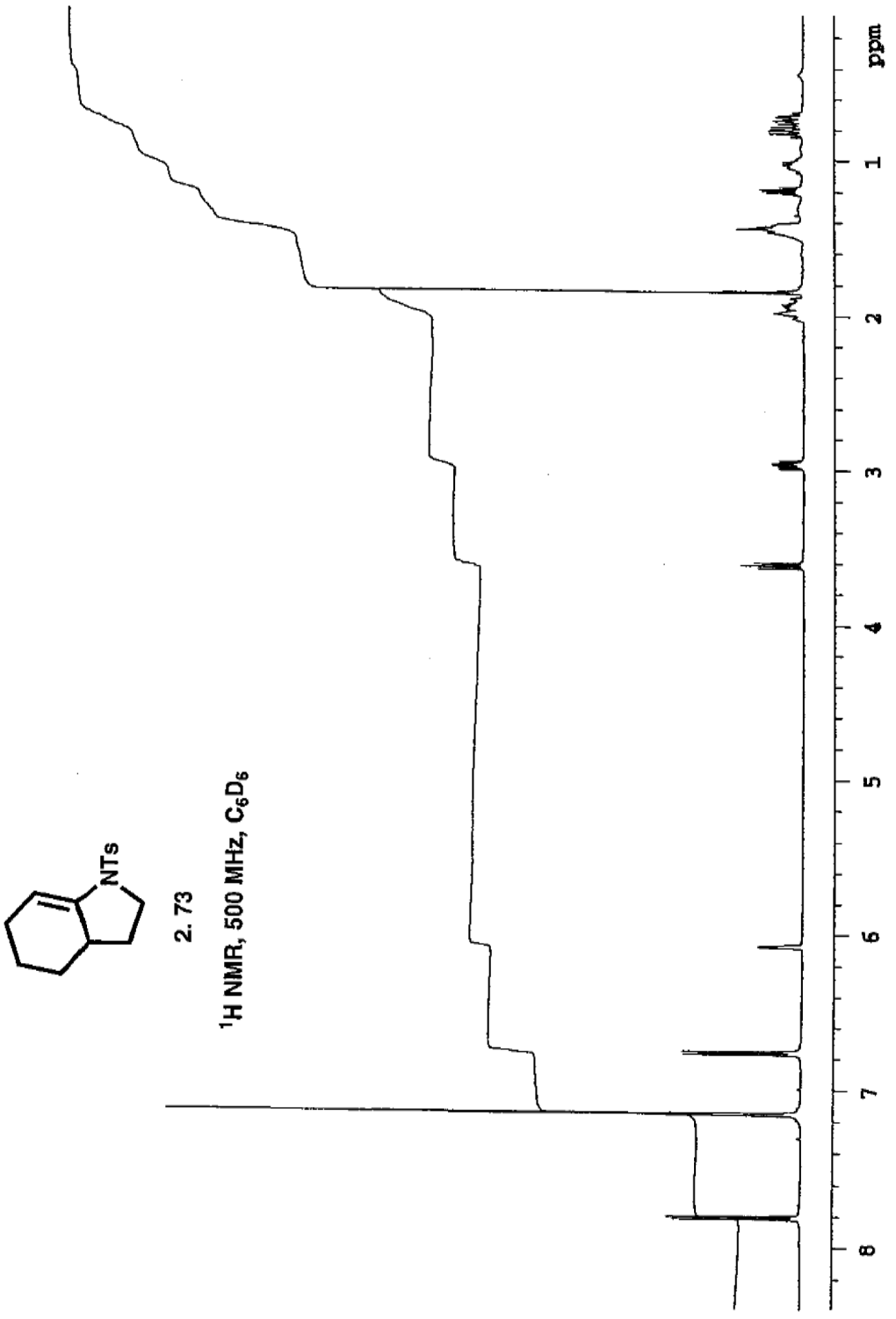


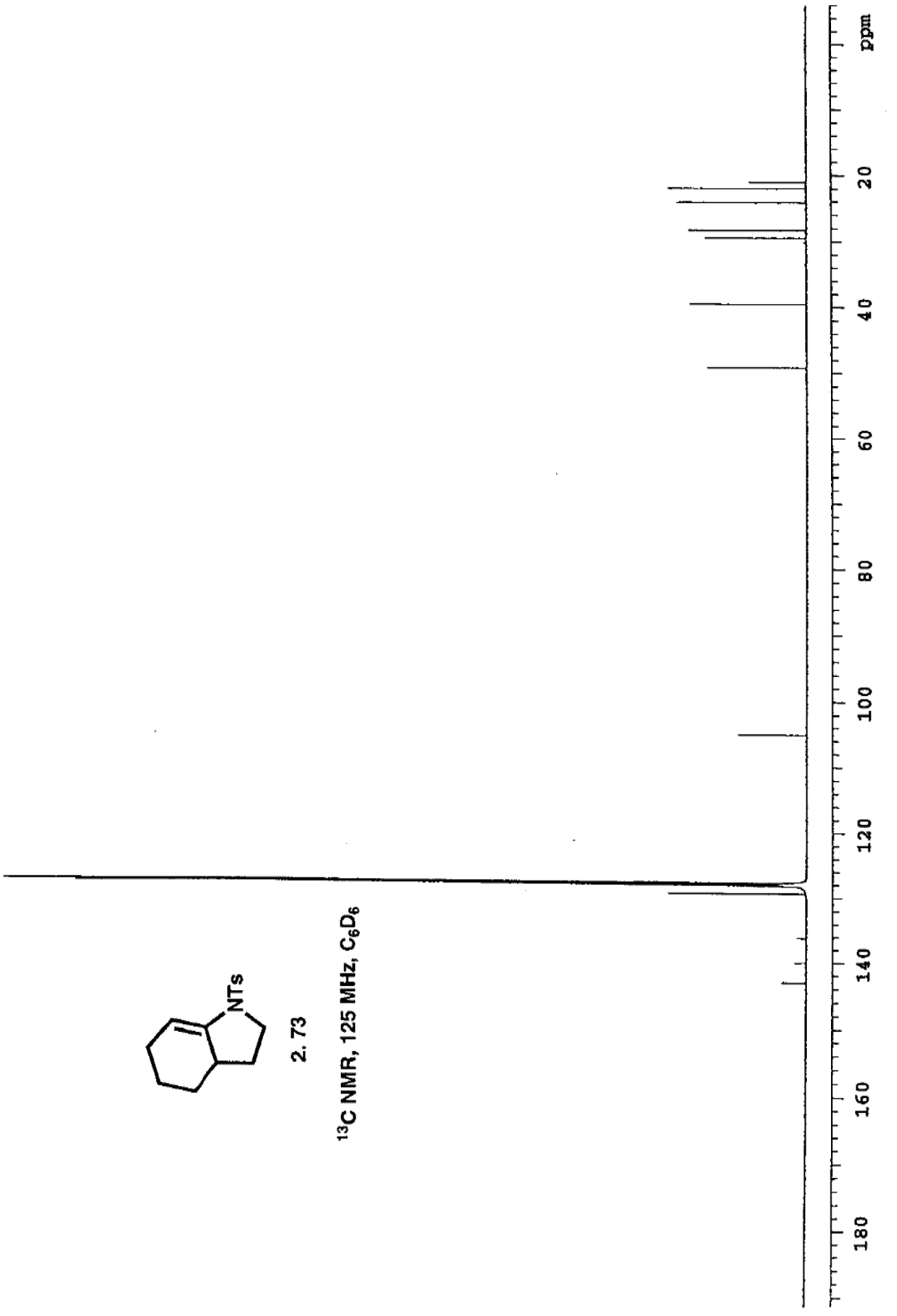

NTs
2. 70
^{1}H NMR, 500 MHz, C_6D_6
ppm
8
7
6
5
4
3
2
1

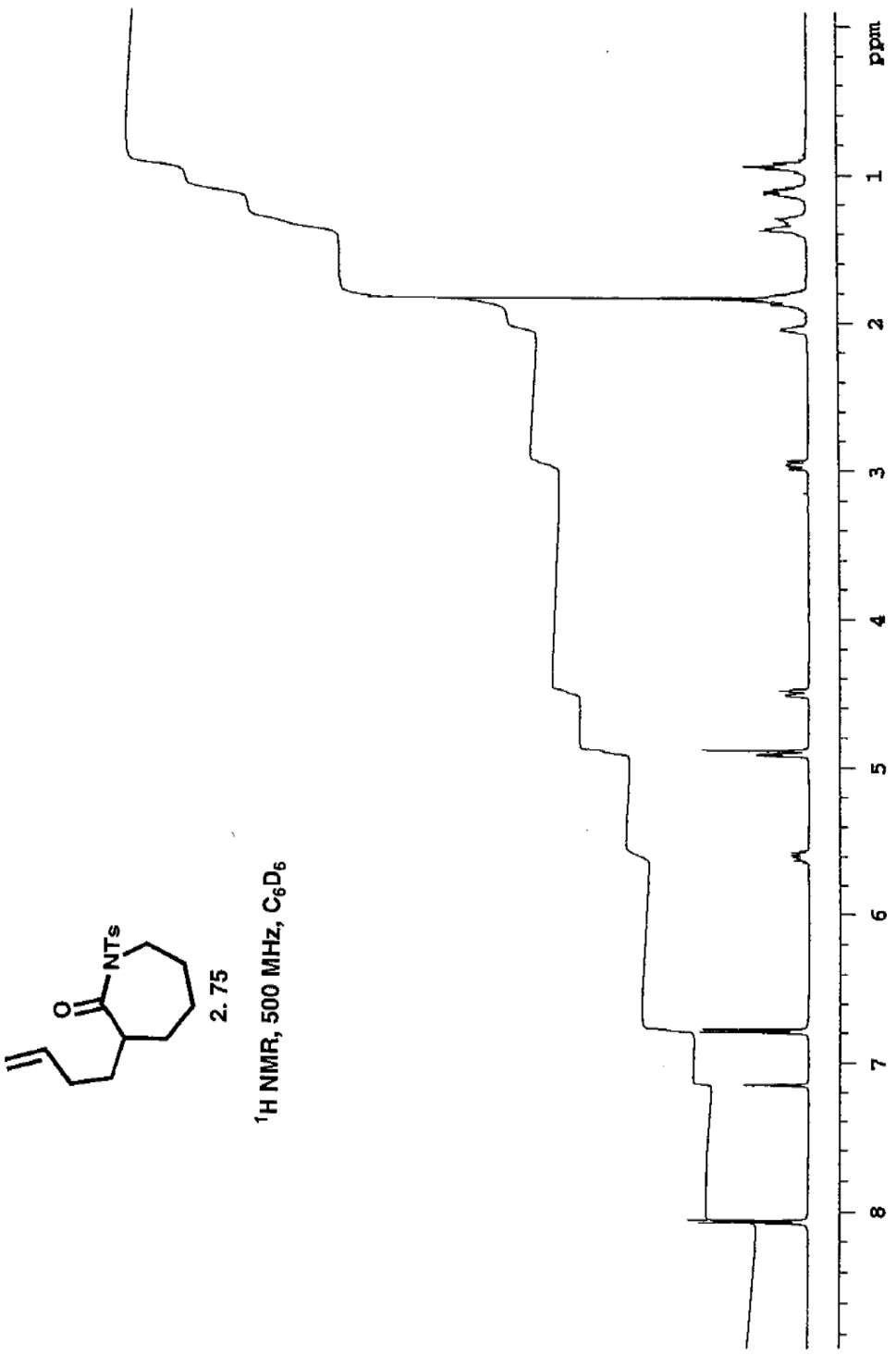

NTs
2.70
^{13}C NMR, 125 MHz, C_6D_6
ppm
180
160
140
120
100
80
60
40
20

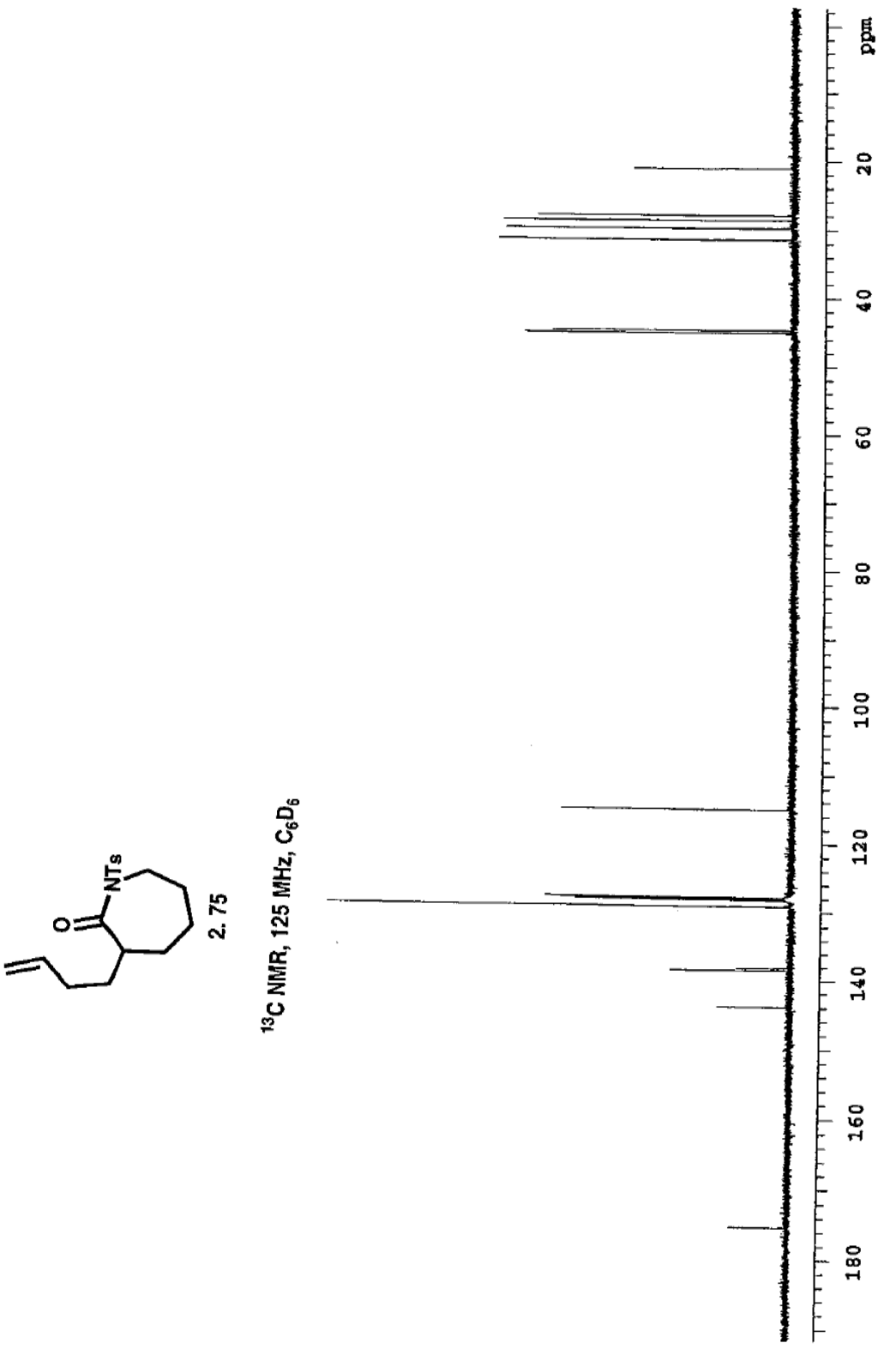

NTs
O
2. 72
^1H NMR, 500 MHz, C_6D_6
ppm
1
2
3
4
5
6
7
8

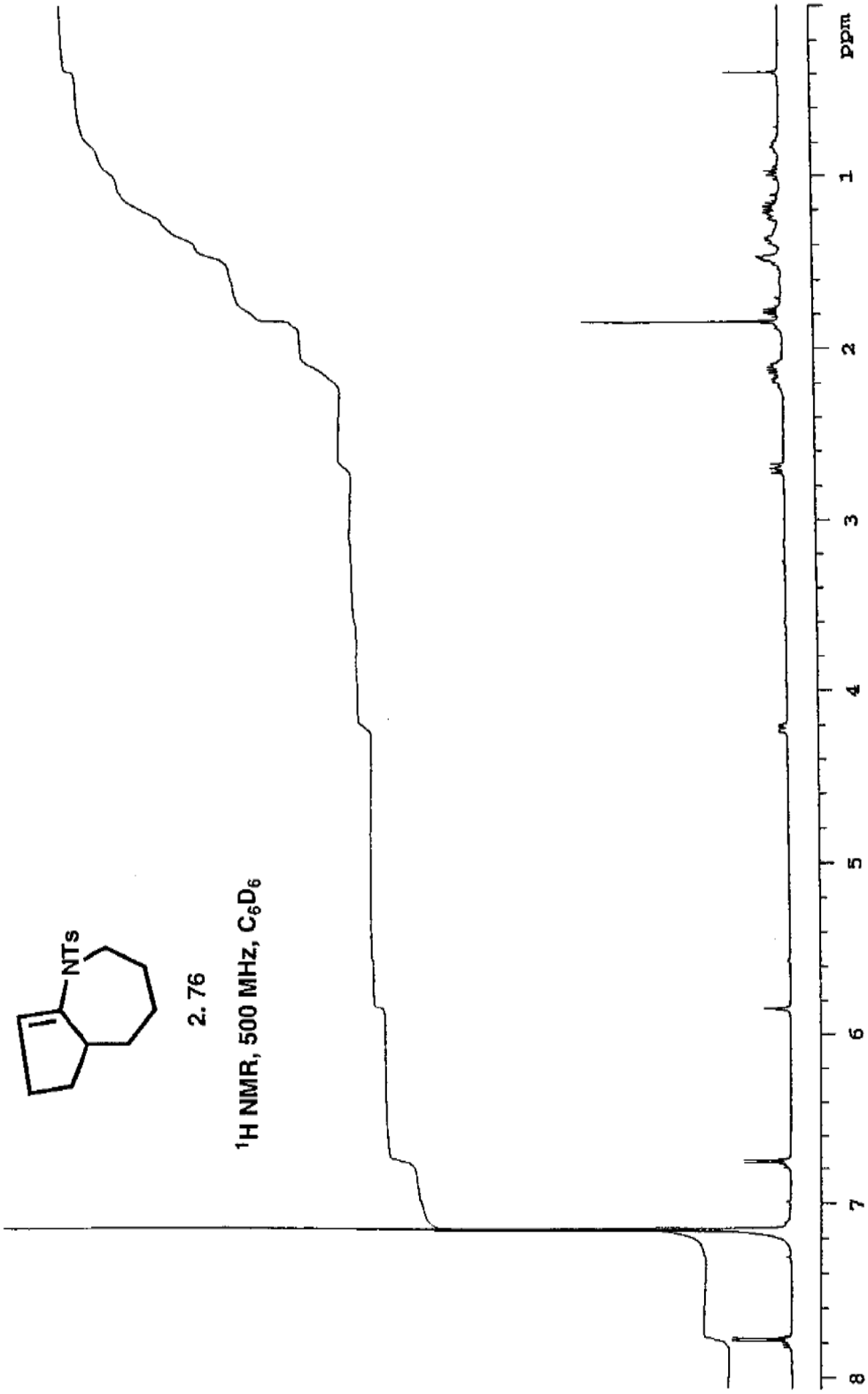

NTs
O
2. 72
^{13}C NMR, 125 MHz, C_6D_6
ppm
180
160
140
120
100
80
60
40
20

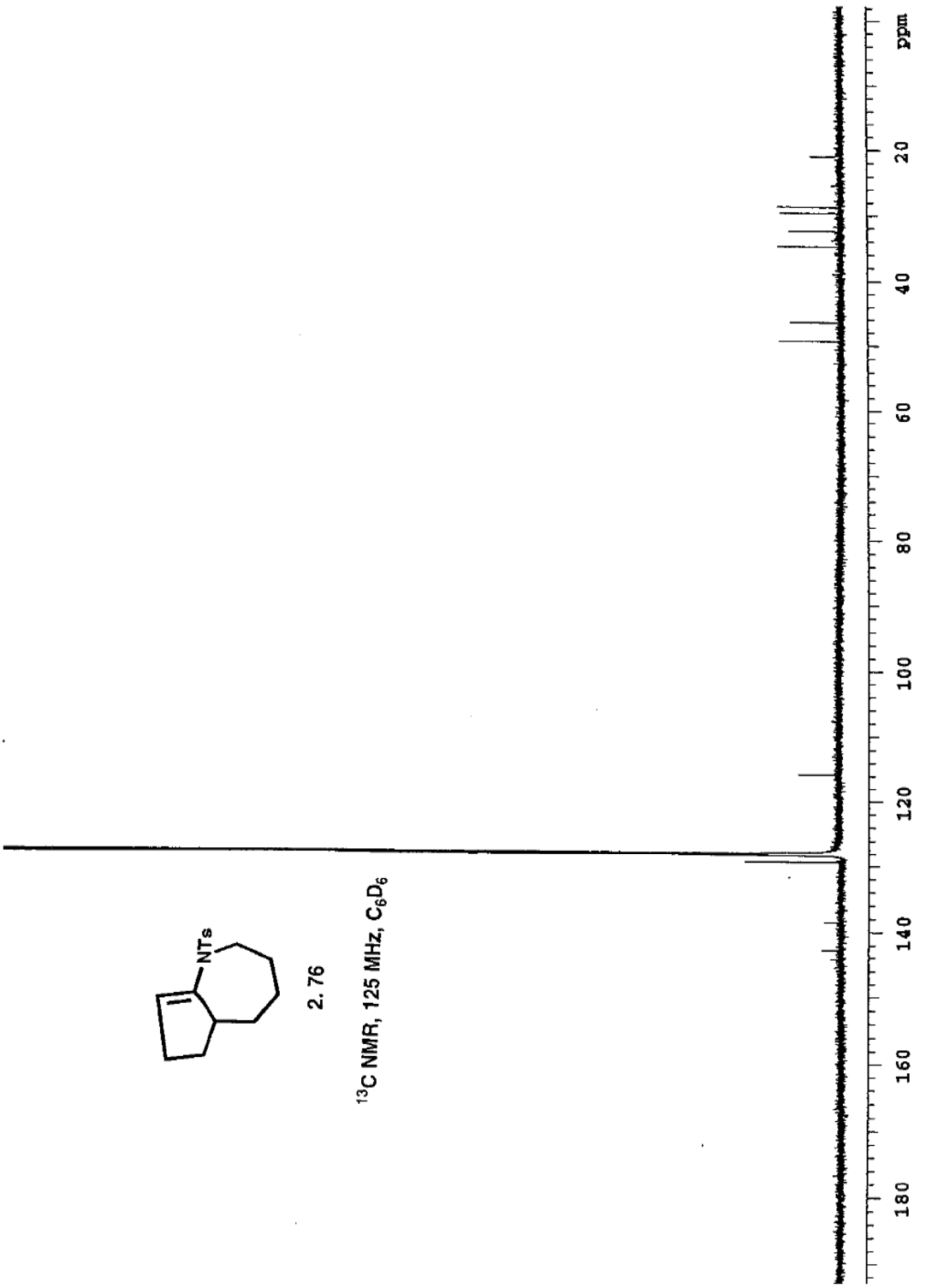

NTs
2. 73
^{1}H NMR, 500 MHz, C_6D_6
ppm
1
2
3
4
5
6
7
8

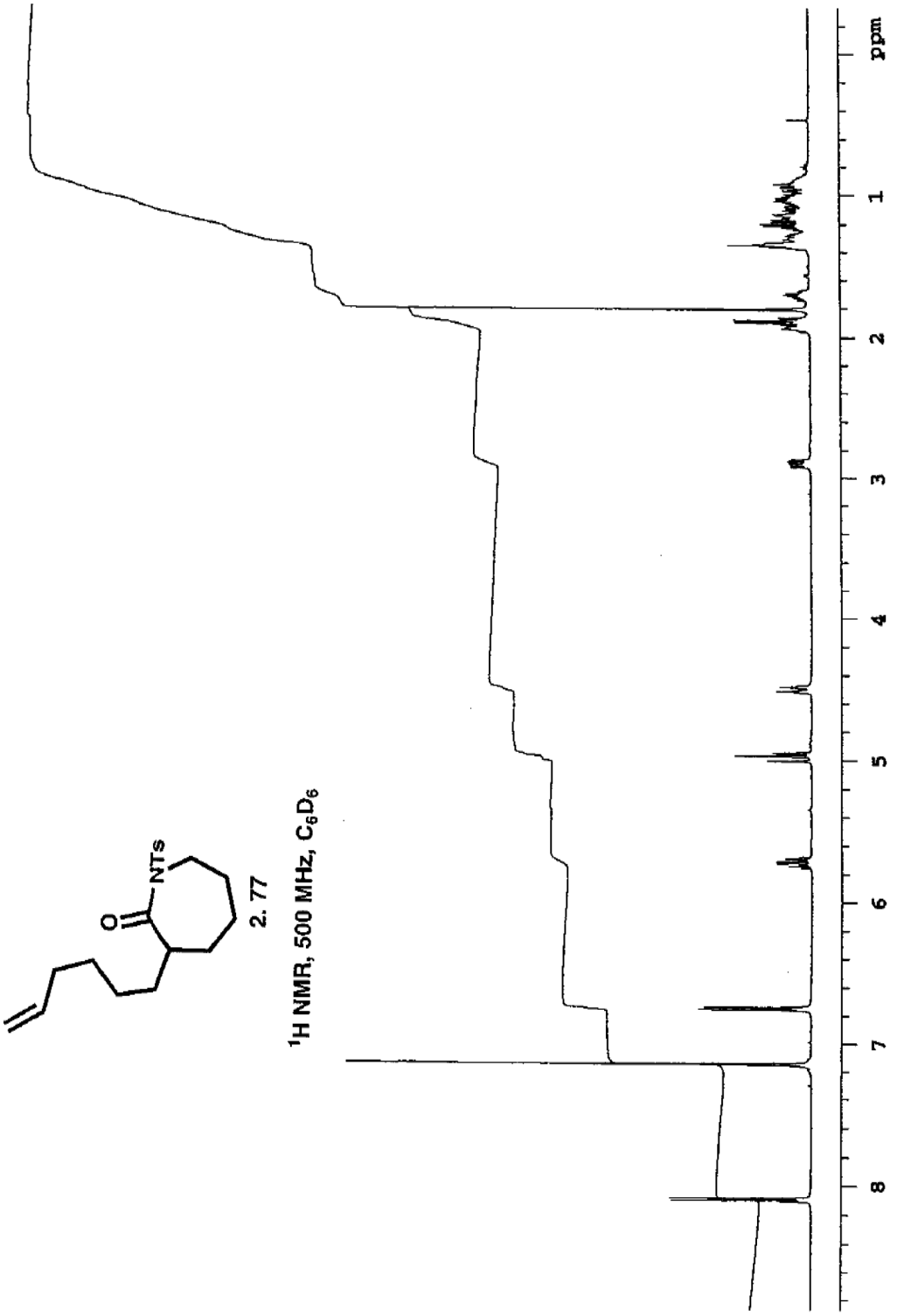

NTs
2. 73
^{13}C NMR, 125 MHz, C_6D_6
ppm
180
160
140
120
100
80
60
40
20

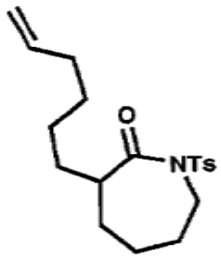

NTs
O
2. 75
^{1}H NMR, 500 MHz, C_6D_6
ppm
1
2
3
4
5
6
7
8


NTs
O
2. 75
^{13}C NMR, 125 MHz, C_6D_6
ppm
20
40
60
80
100
120
140
160
180


NTs
2. 76
^{1}H NMR, 500 MHz, C_6D_6
ppm
1
2
3
4
5
6
7
8

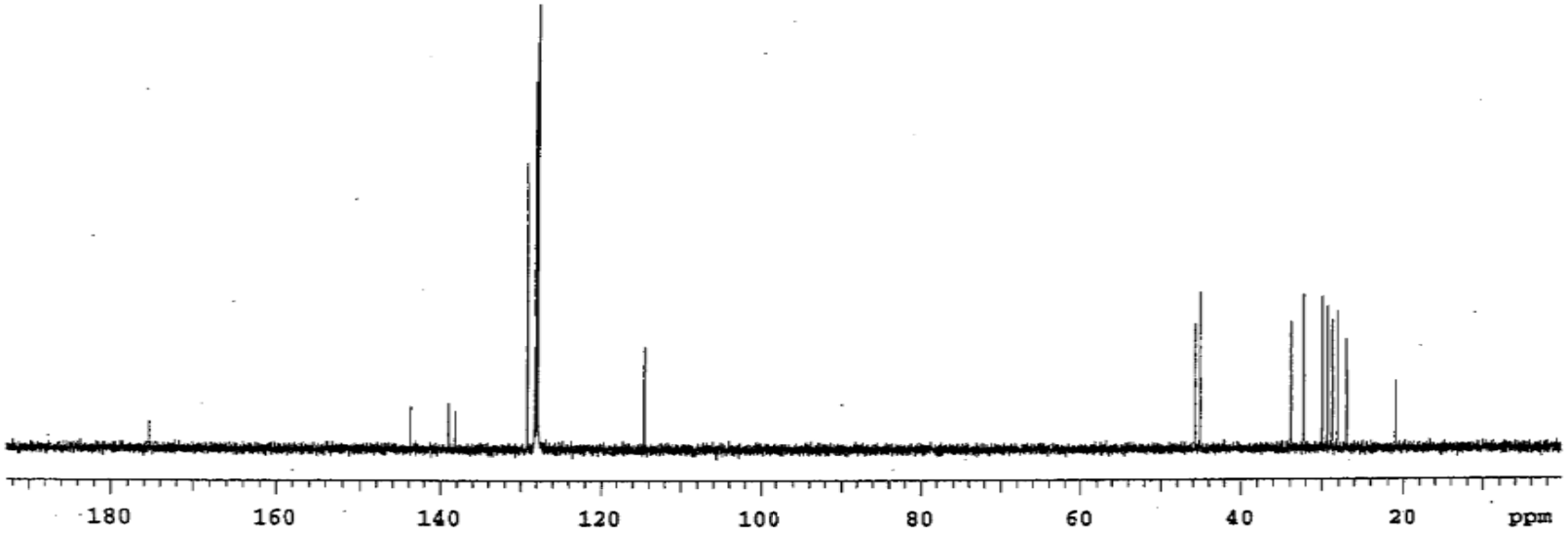

NTs
2. 76
^{13}C NMR, 125 MHz, C_6D_6
180
160
140
120
100
80
60
40
20
ppm

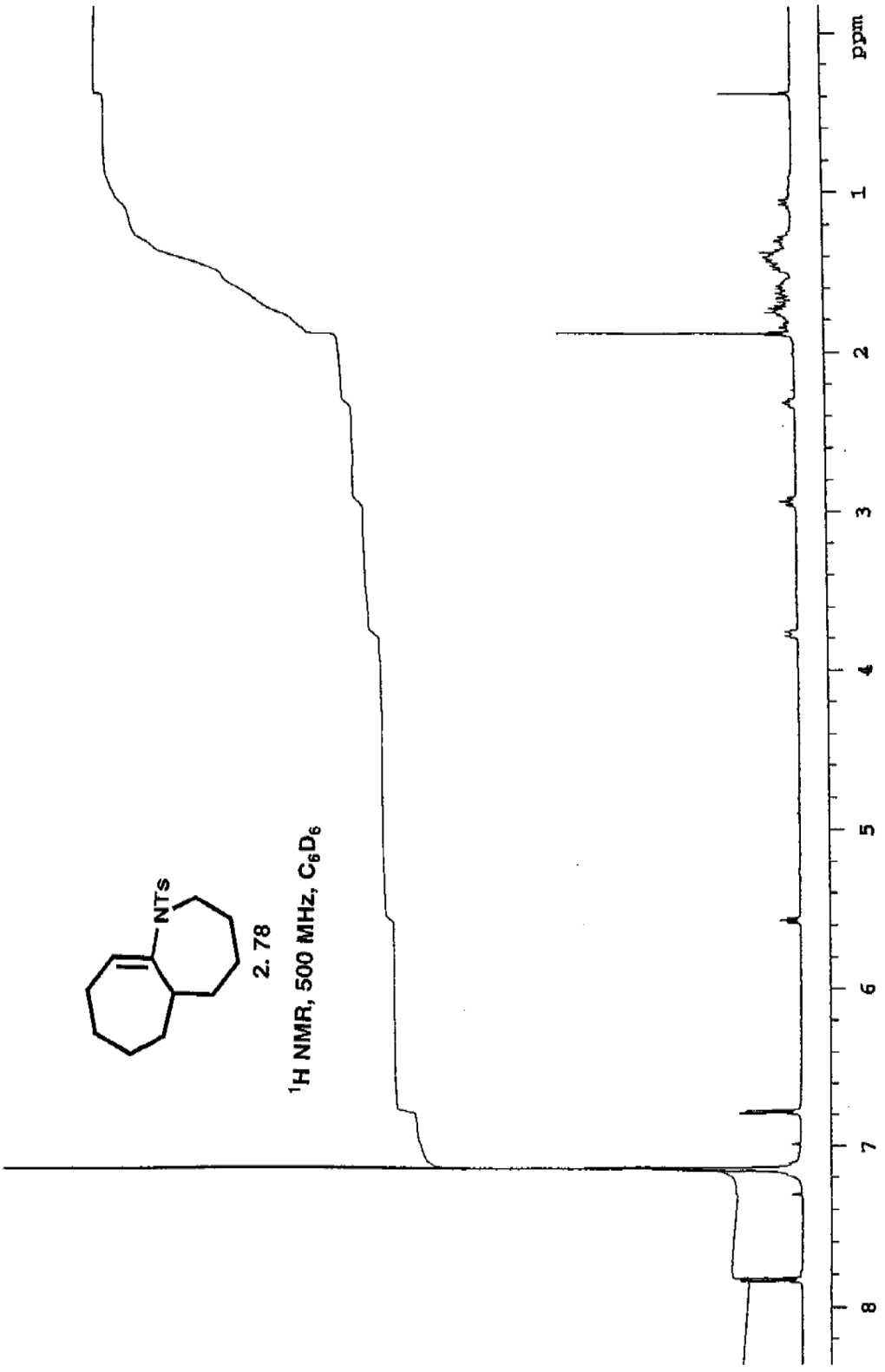

NTs
O
2. 77
^{1}H NMR, 500 MHz, C_6D_6
ppm
1
2
3
4
5
6
7
8

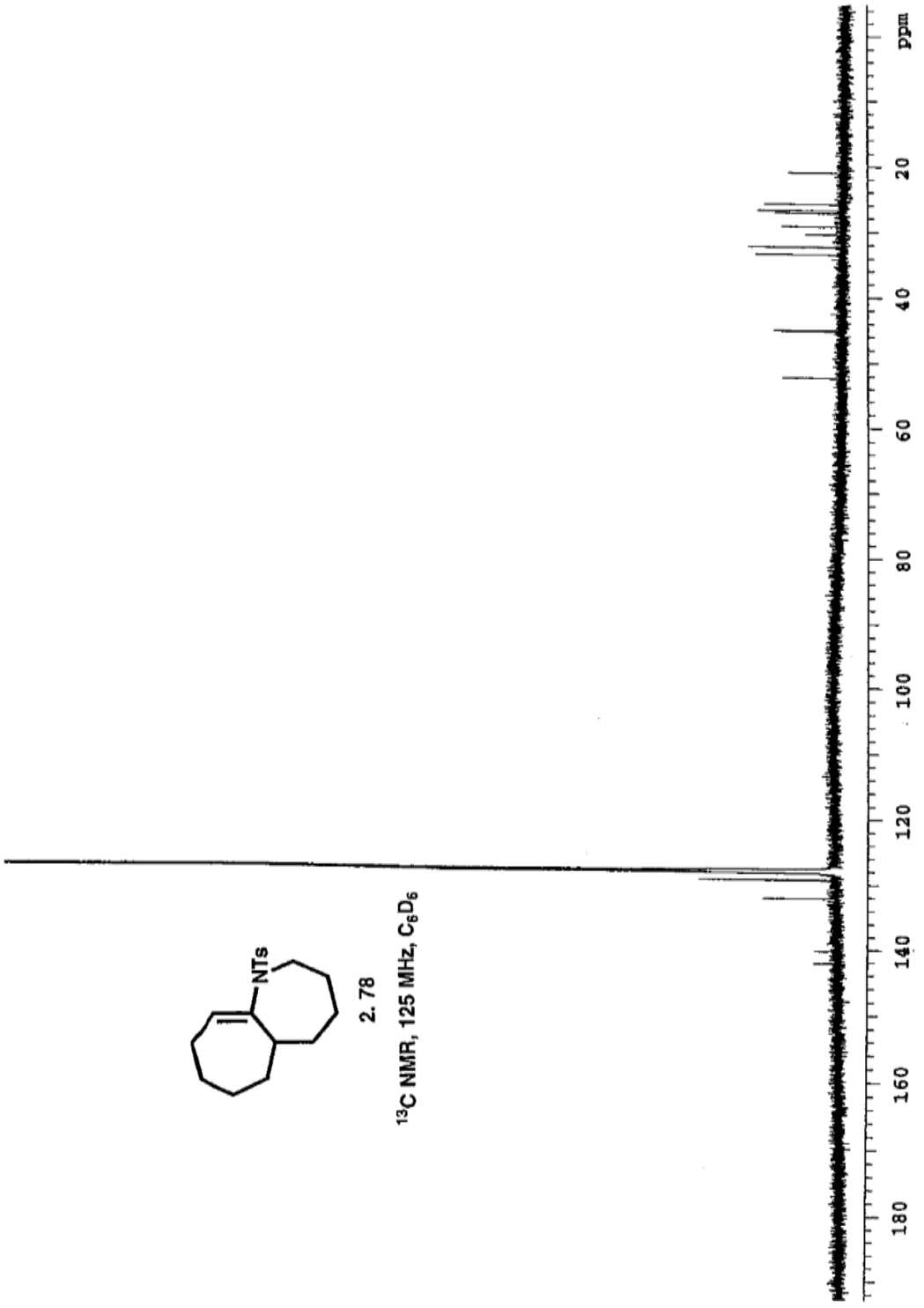


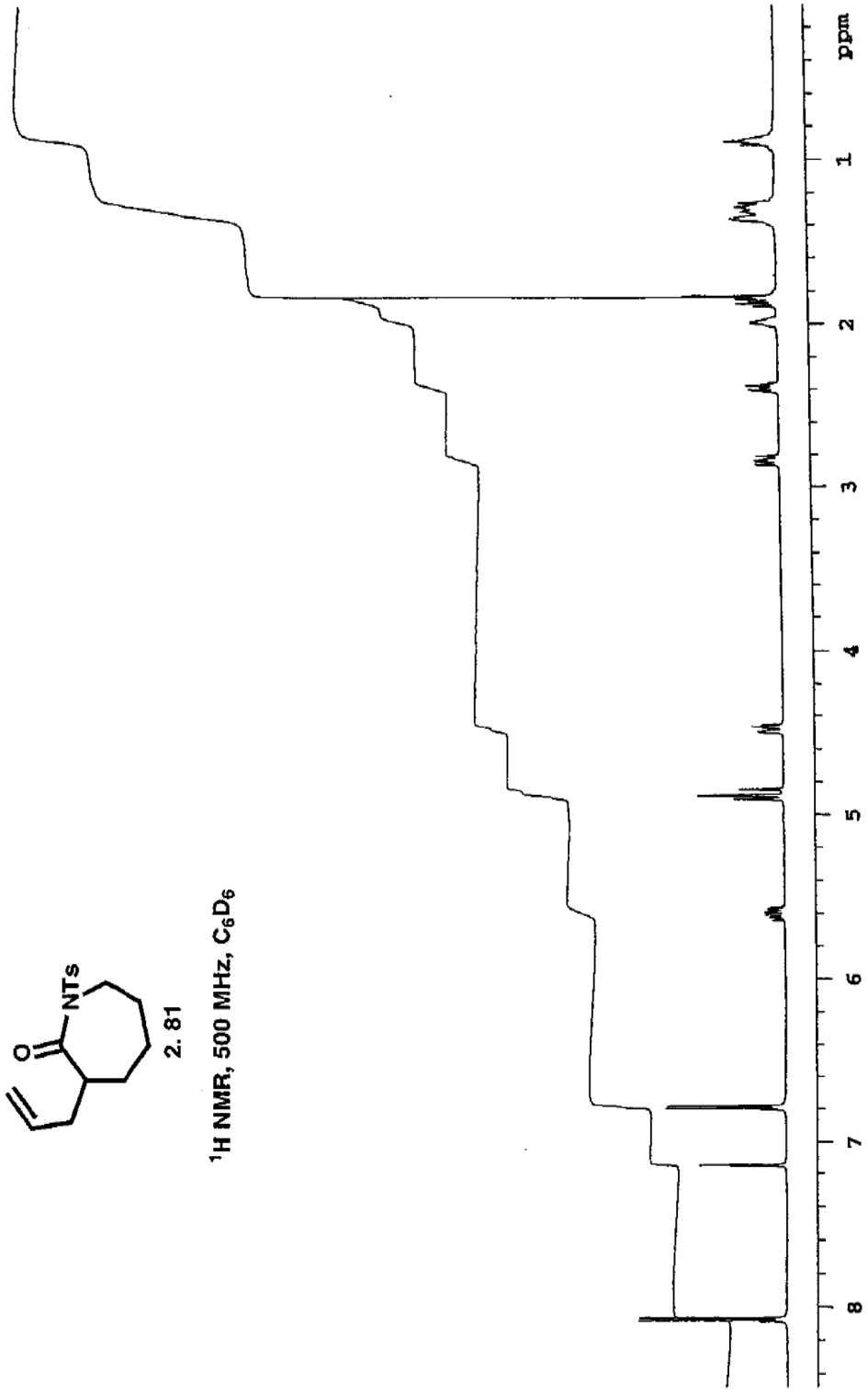
2. 77

^{13}C NMR, 125 MHz, C_6D_6



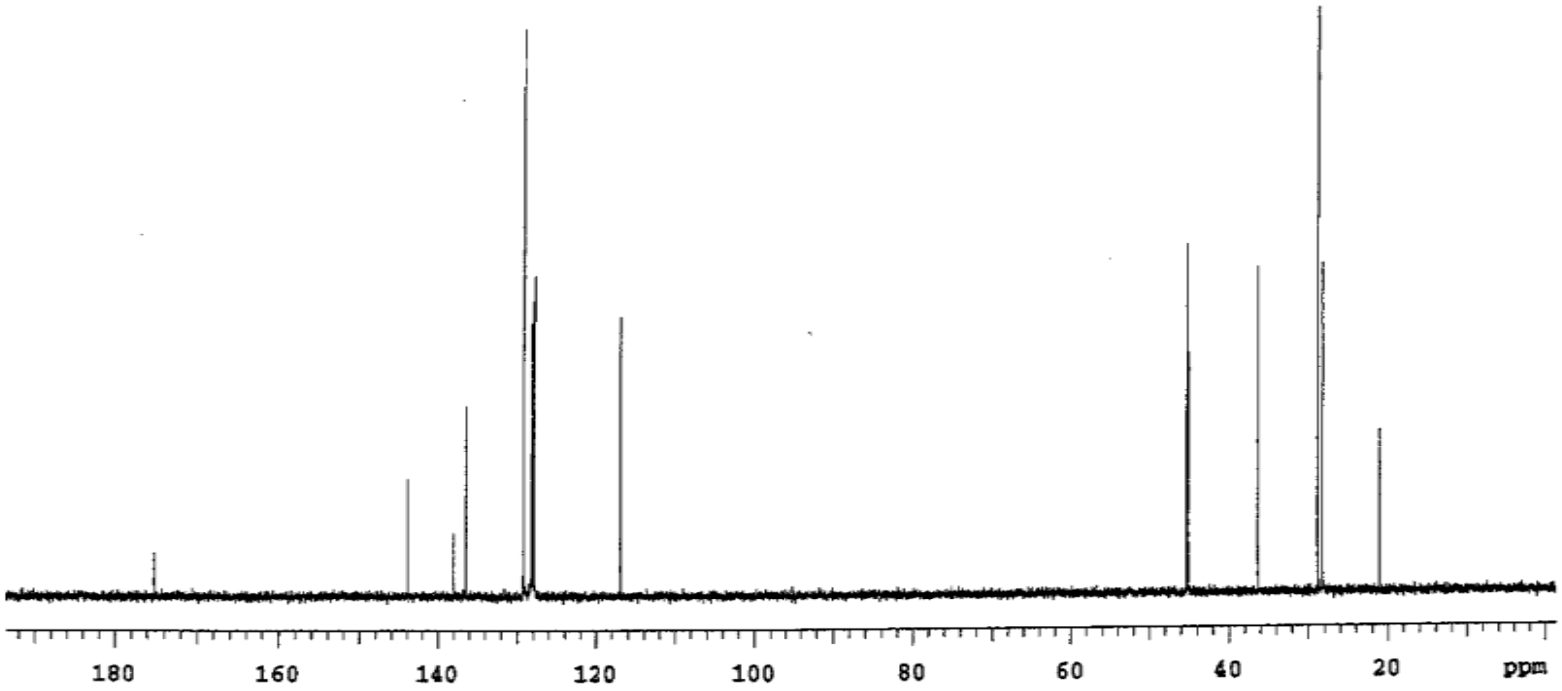

NTs
2. 78
^{1}H NMR, 500 MHz, C_6D_6
ppm
1
2
3
4
5
6
7
8

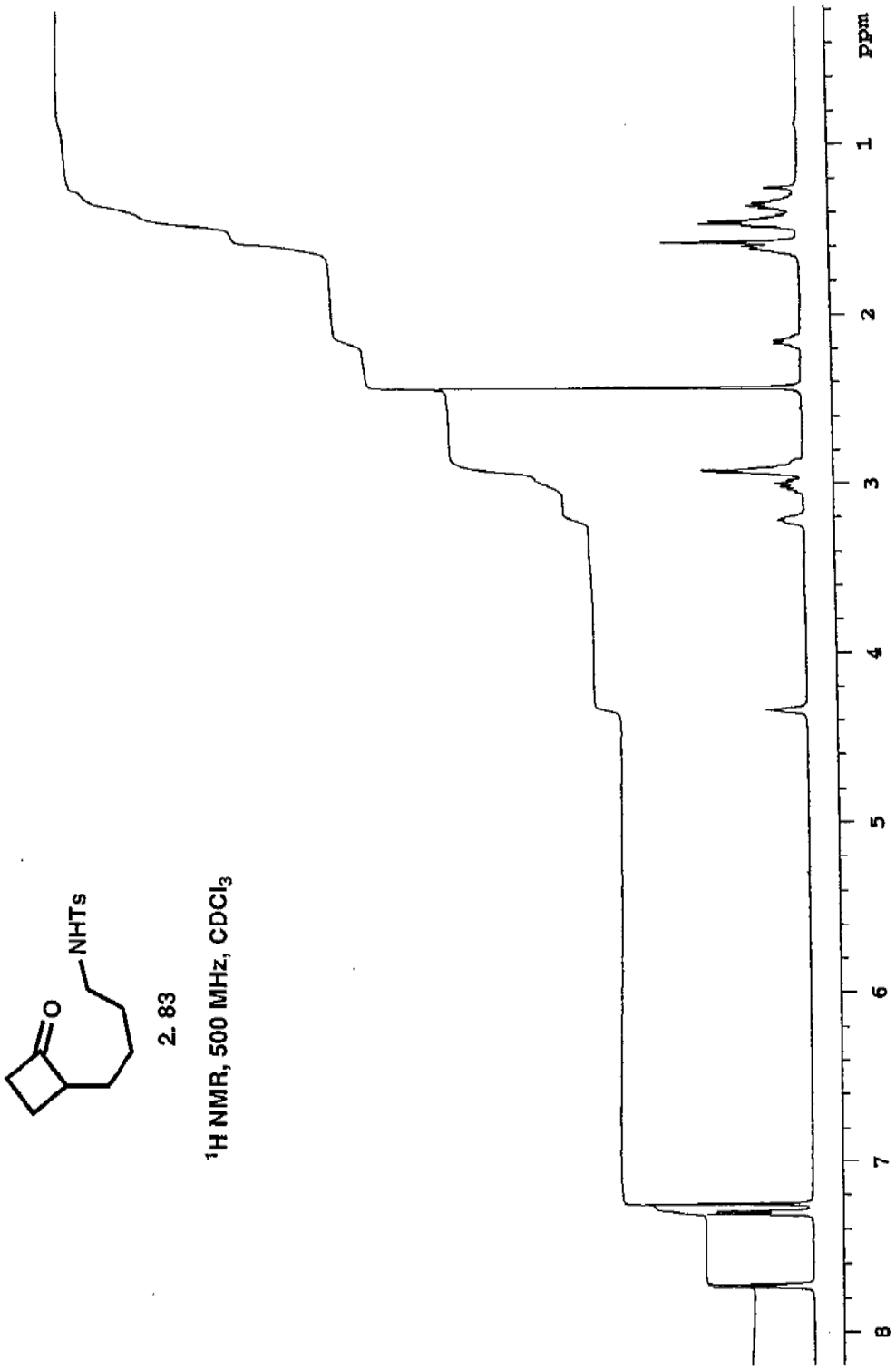

NTs
2. 78
^{13}C NMR, 125 MHz, C_6D_6
ppm
180
160
140
120
100
80
60
40
20

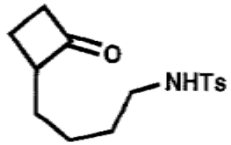

NTs
O
2. 81
^{1}H NMR, 500 MHz, C_6D_6
ppm
1
2
3
4
5
6
7
8

2. 81

^{13}C NMR, 125 MHz, C_6D_6

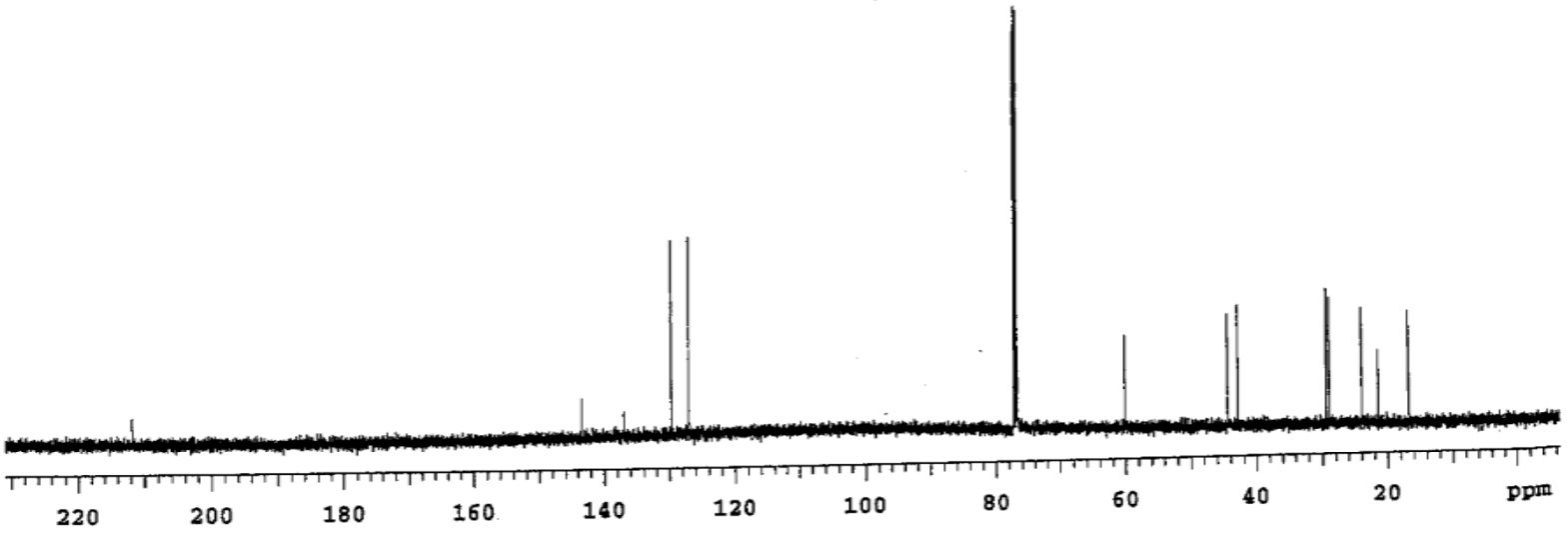


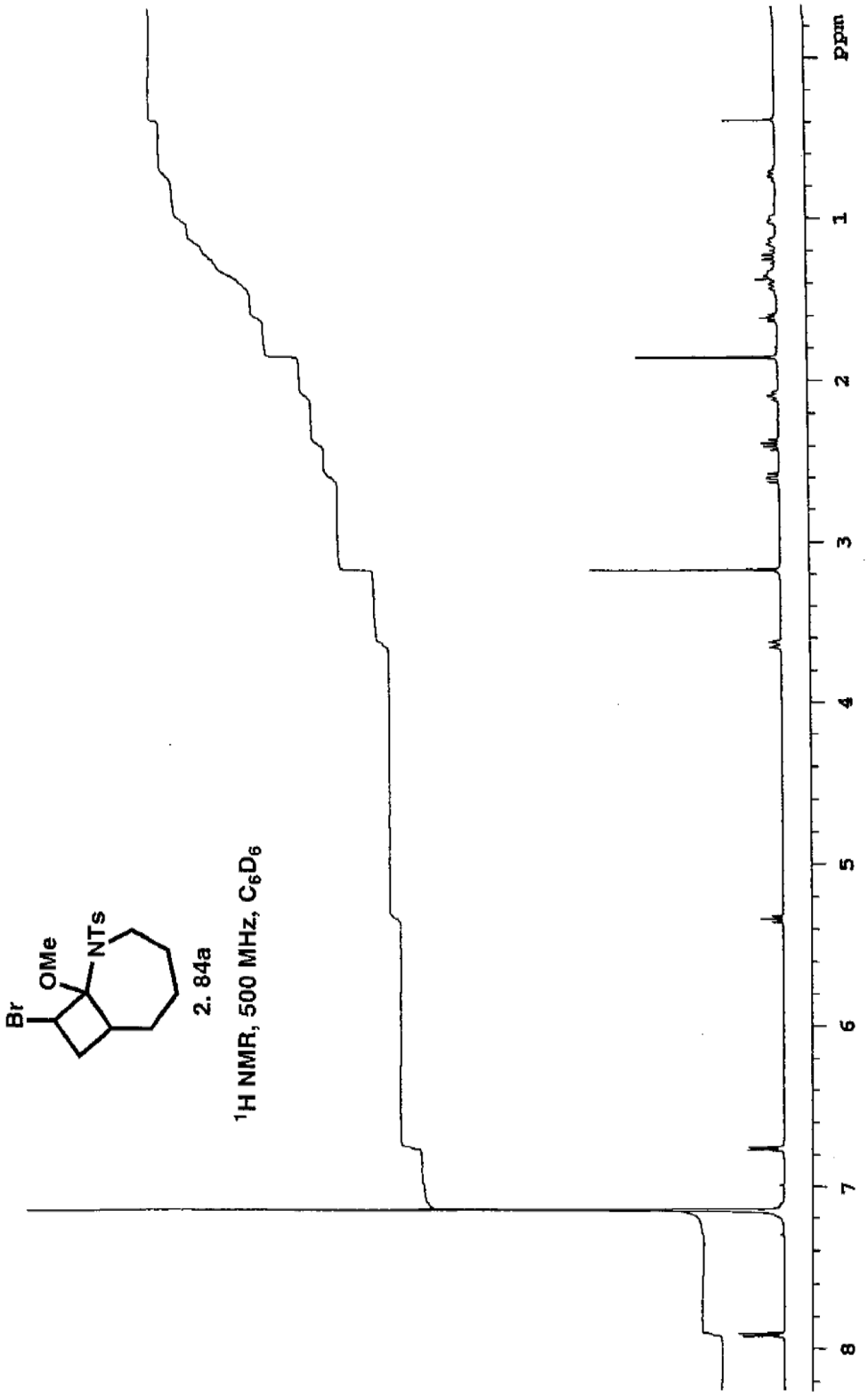

NHTs
O
2. 83
^{1}H NMR, 500 MHz, $CDCl_3$
ppm
1
2
3
4
5
6
7
8

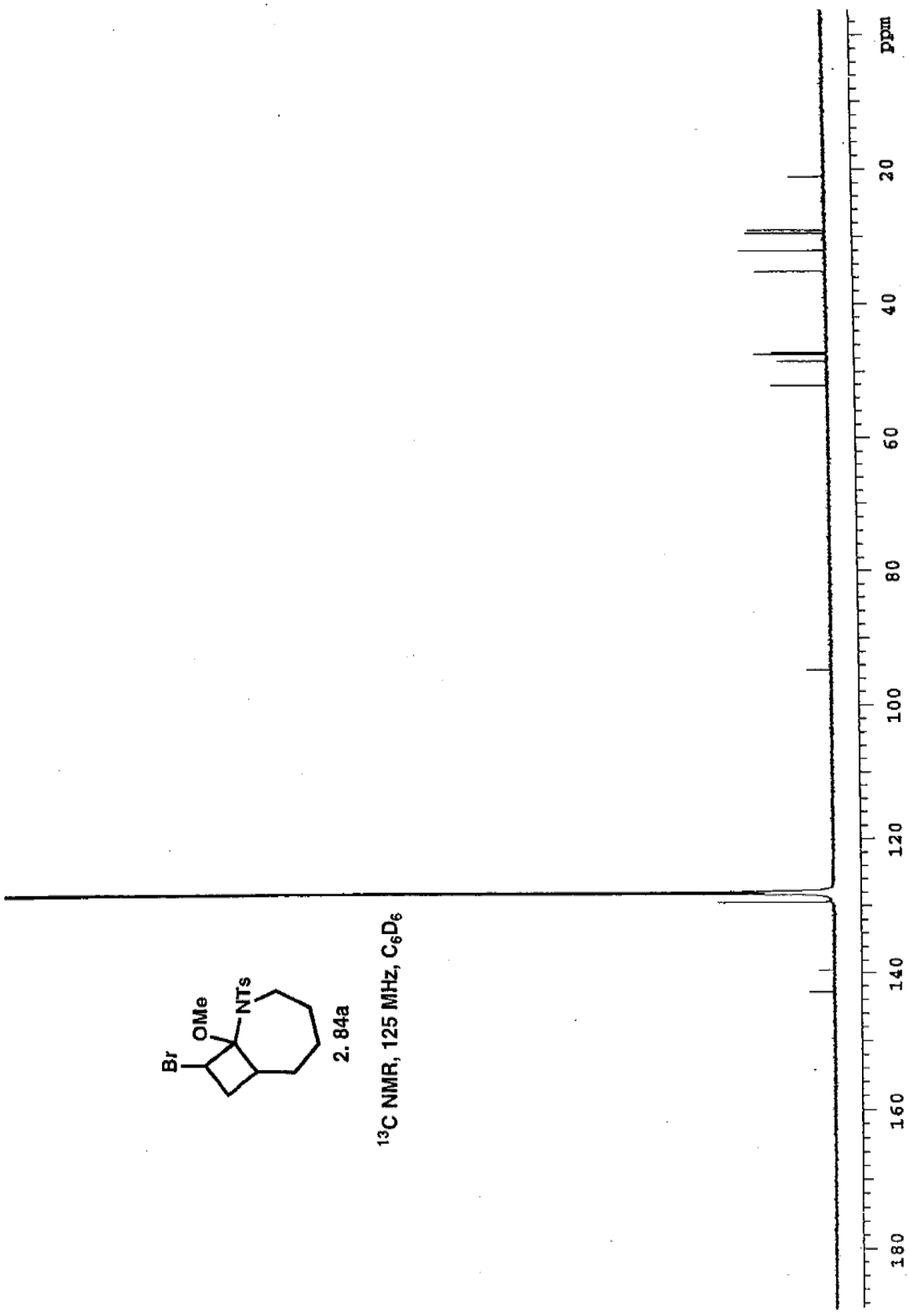


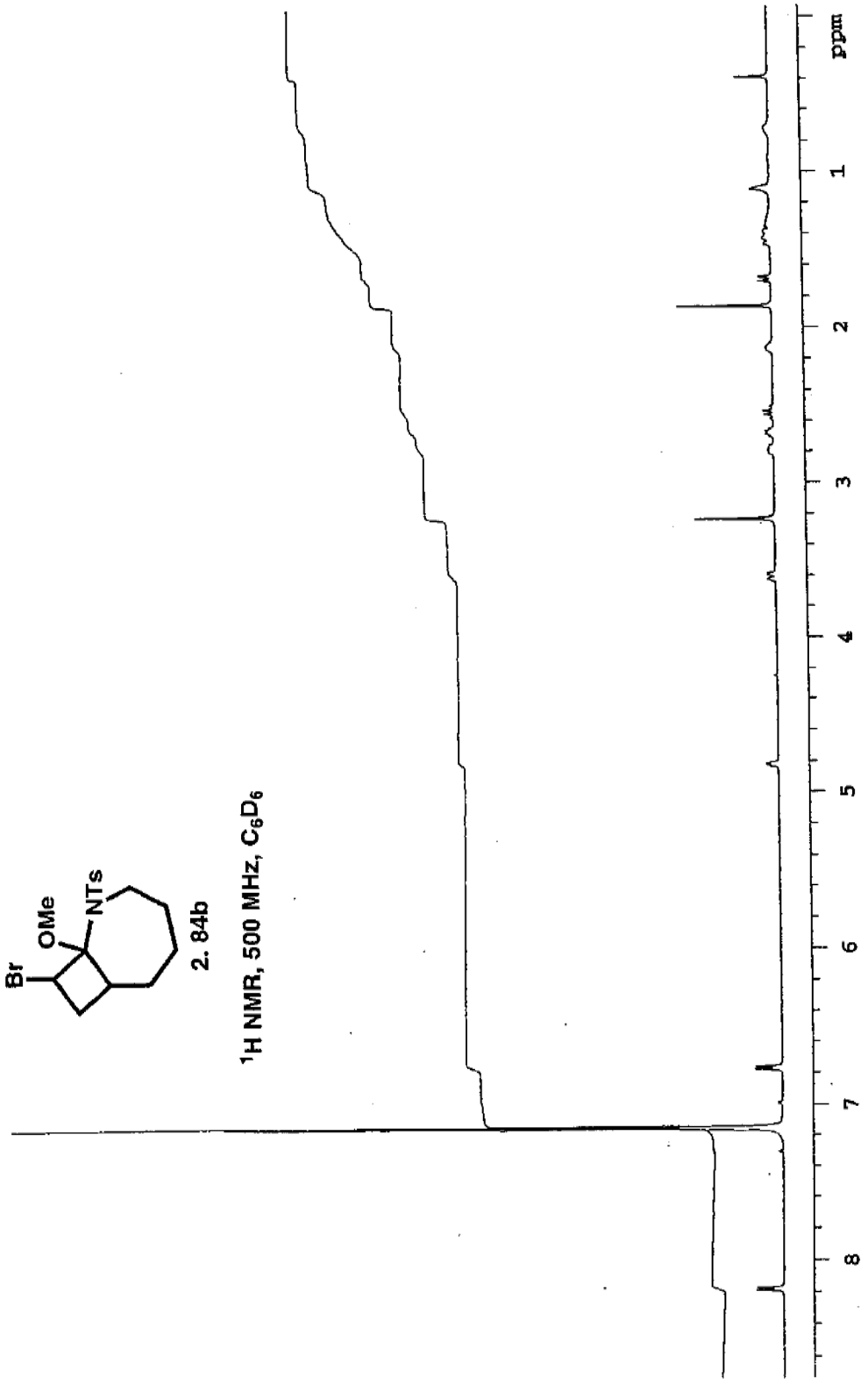
2. 83

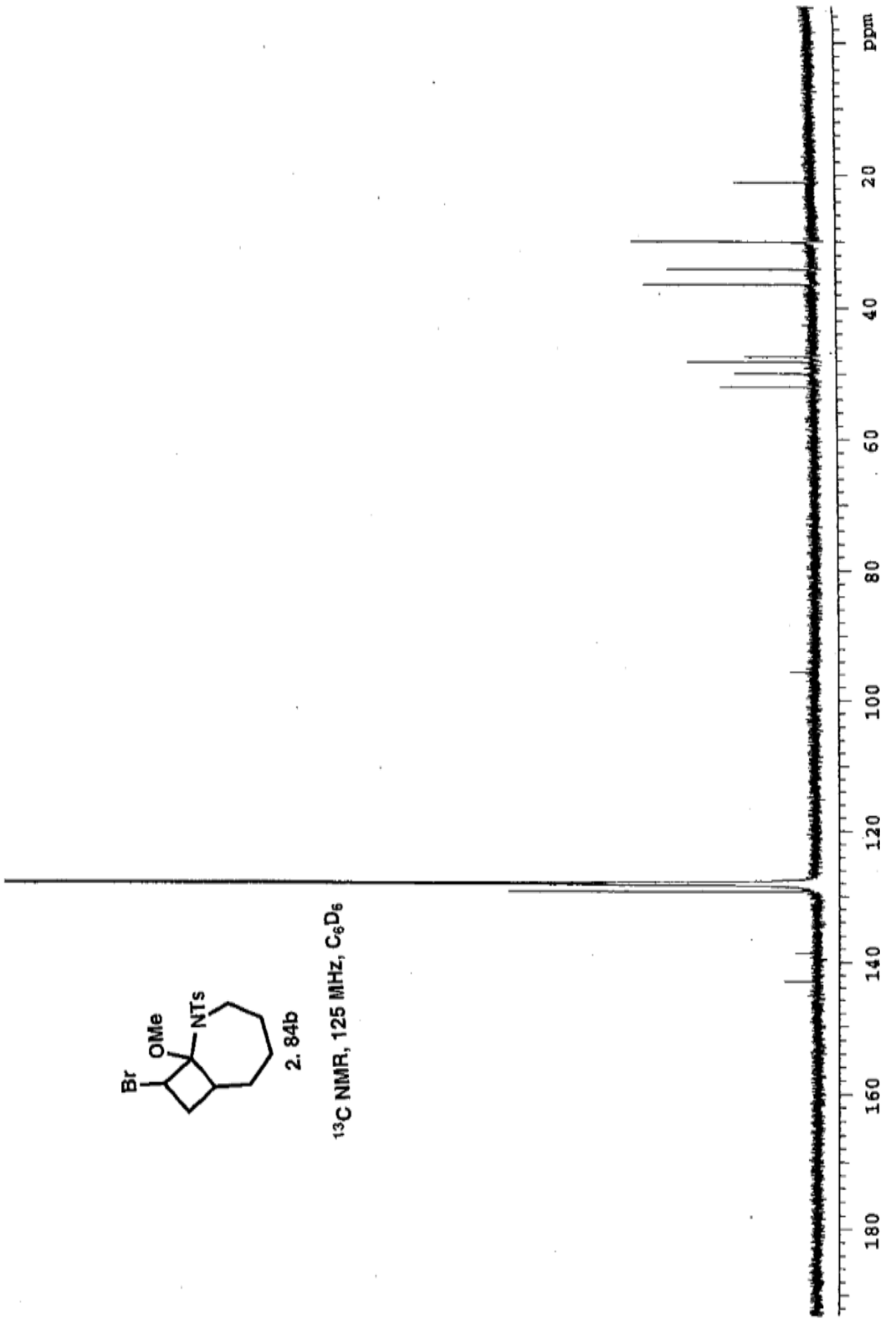
^{13}C NMR, 125 MHz, $CDCl_3$

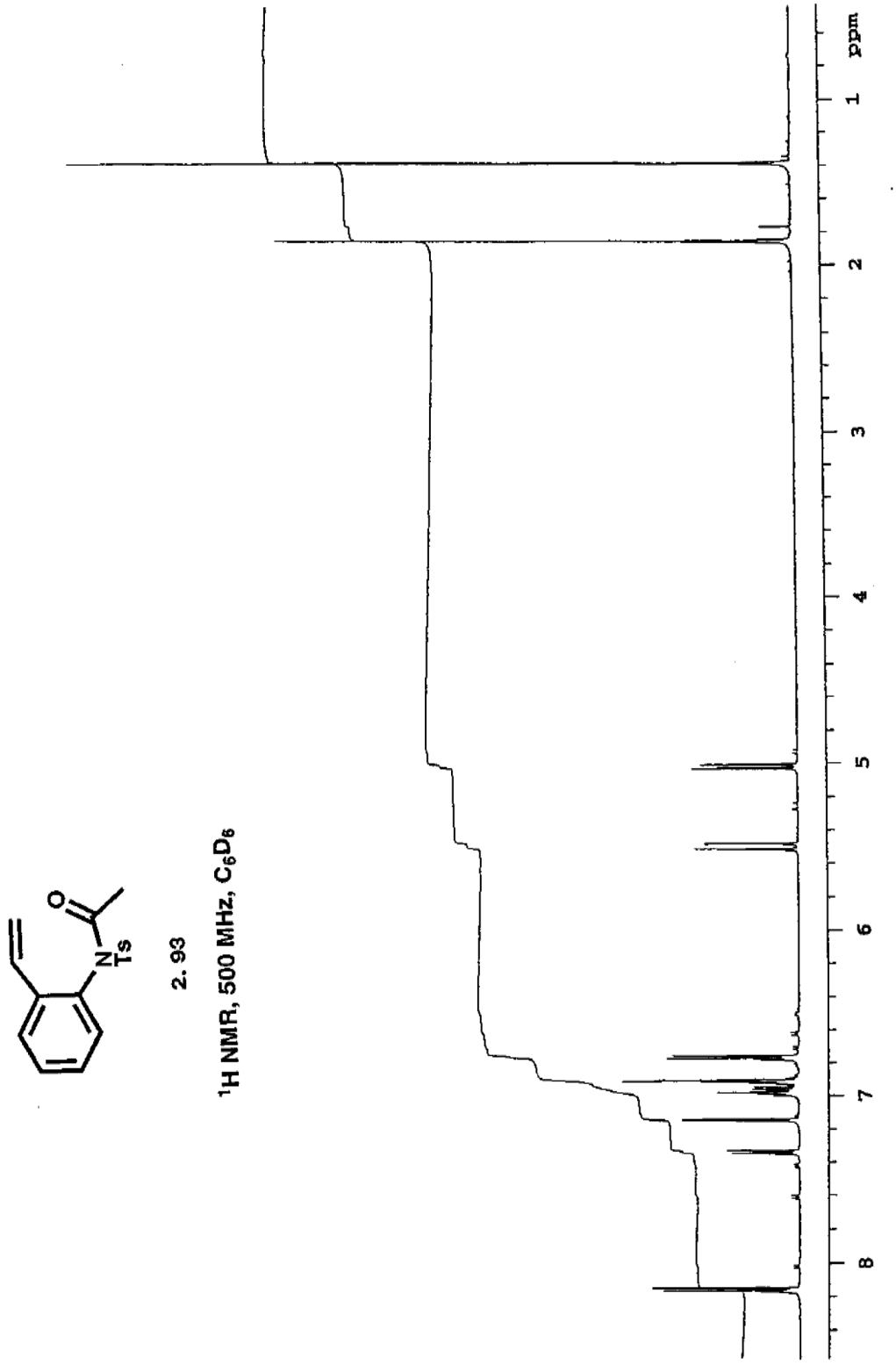


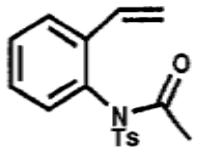

Br
OMe
NTs
2. 84a
^{1}H NMR, 500 MHz, C_6D_6
ppm
1
2
3
4
5
6
7
8


Br
OMe
NTs
2. 84a
^{13}C NMR, 125 MHz, C_6D_6
ppm
180
160
140
120
100
80
60
40
20


Br
OMe
NTs
2. 84b
^{1}H NMR, 500 MHz, C_6D_6
ppm
1
2
3
4
5
6
7
8

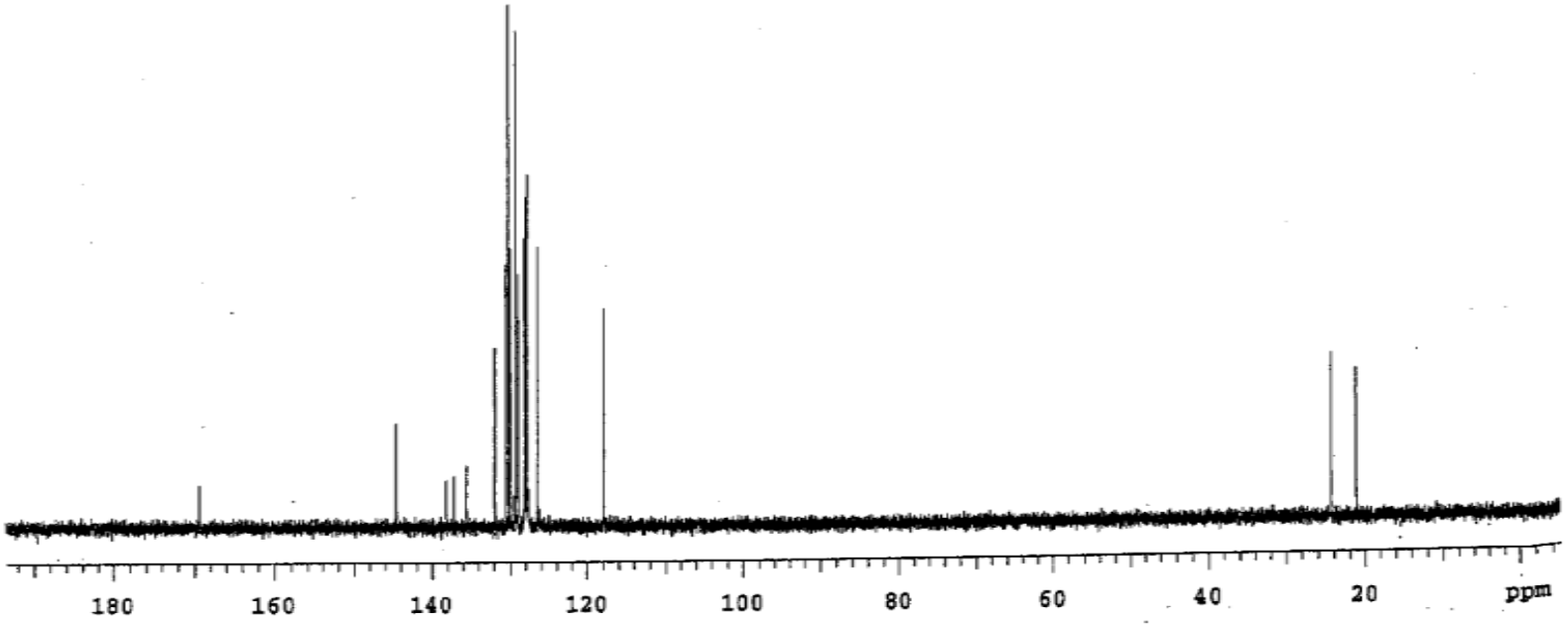

Br
OMe
NTs
2. 84b
^{13}C NMR, 125 MHz, C_6D_6
ppm
180
160
140
120
100
80
60
40
20

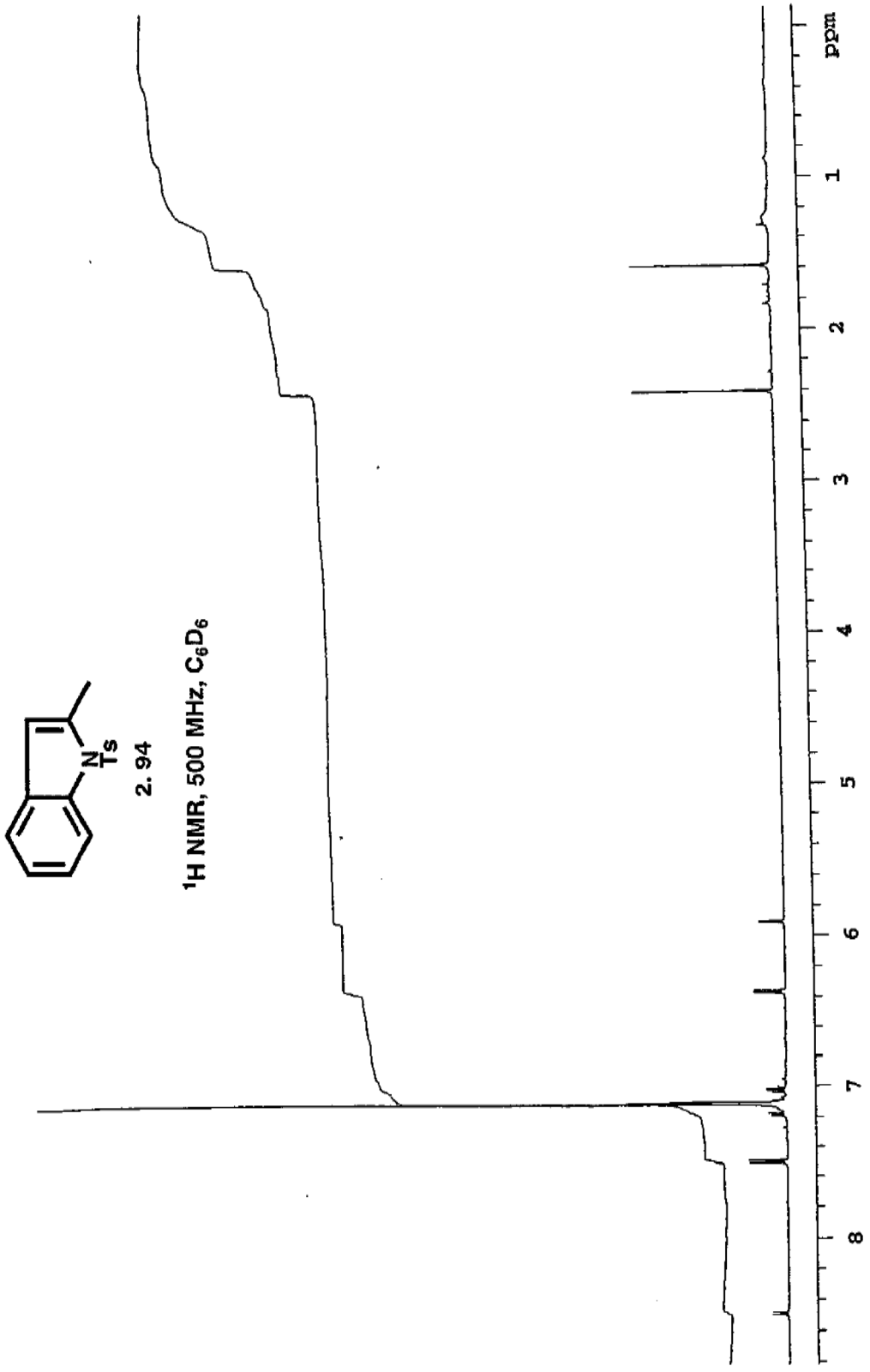

O
N
Ts
2. 93
^{1}H NMR, 500 MHz, C_6D_6
1 ppm
2
3
4
5
6
7
8

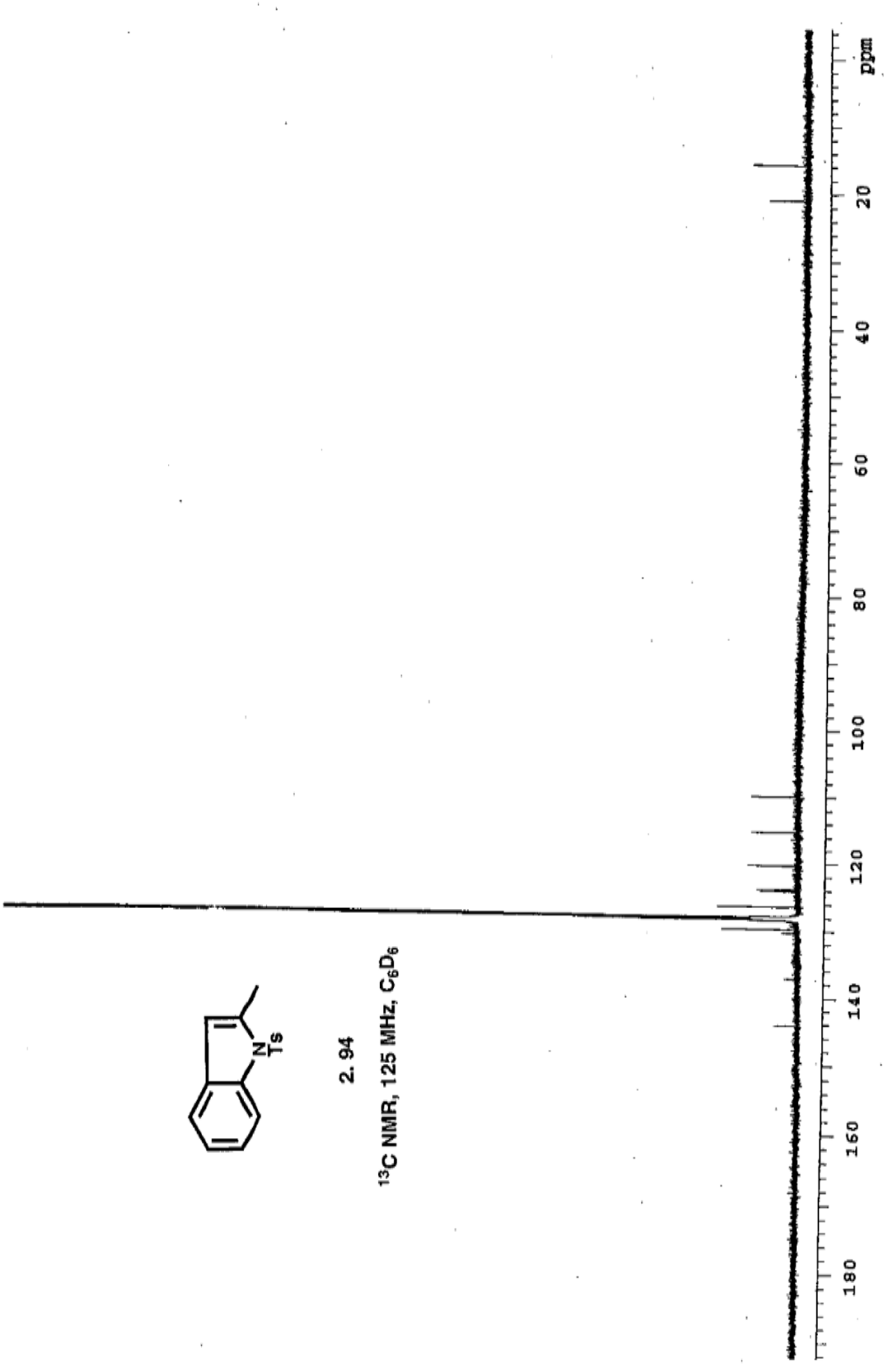


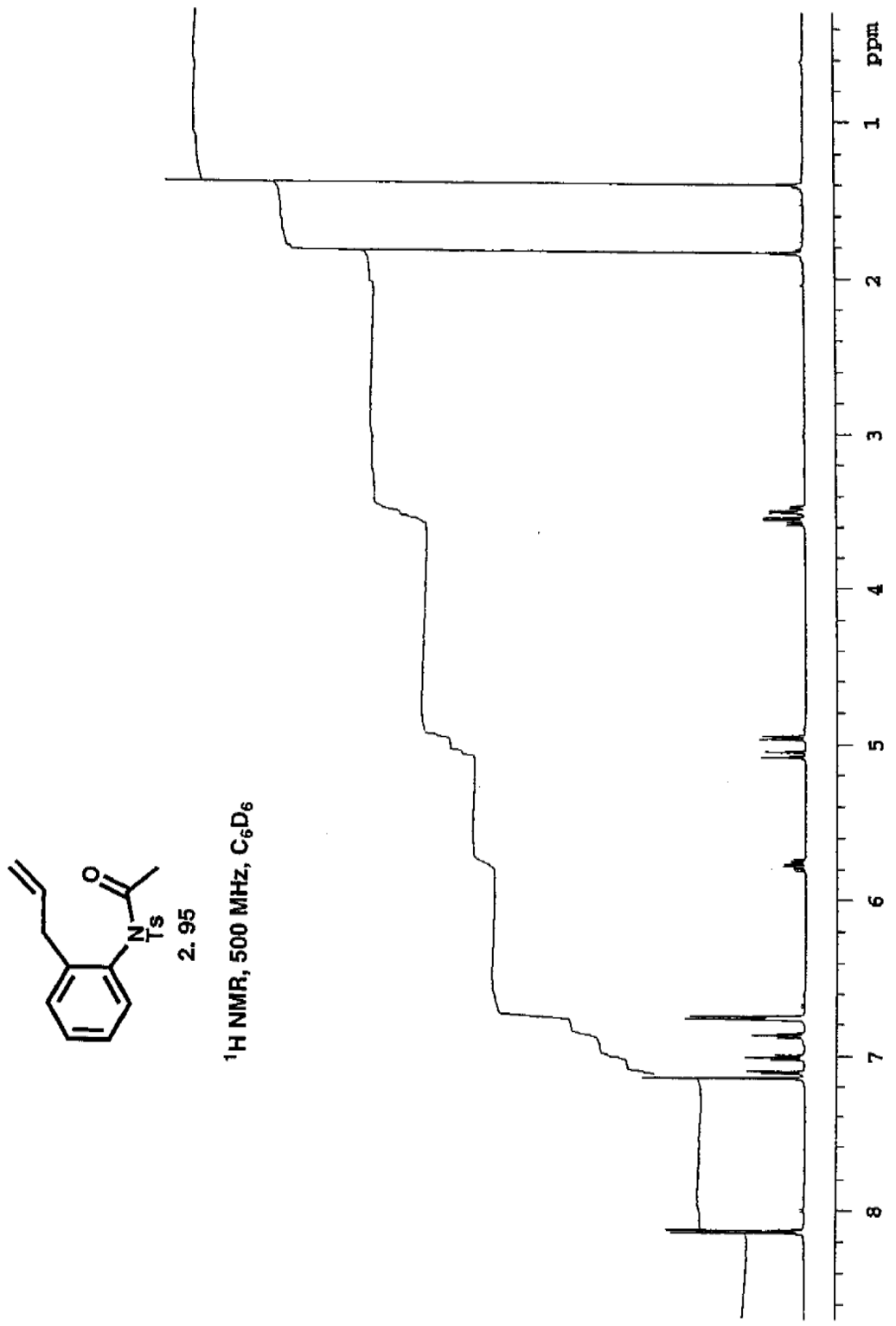
2. 93

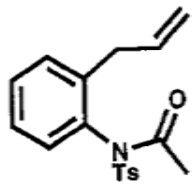
^{13}C NMR, 125 MHz, C_6D_6




N
Ts
2. 94
^{1}H NMR, 500 MHz, C_6D_6
ppm
1
2
3
4
5
6
7
8

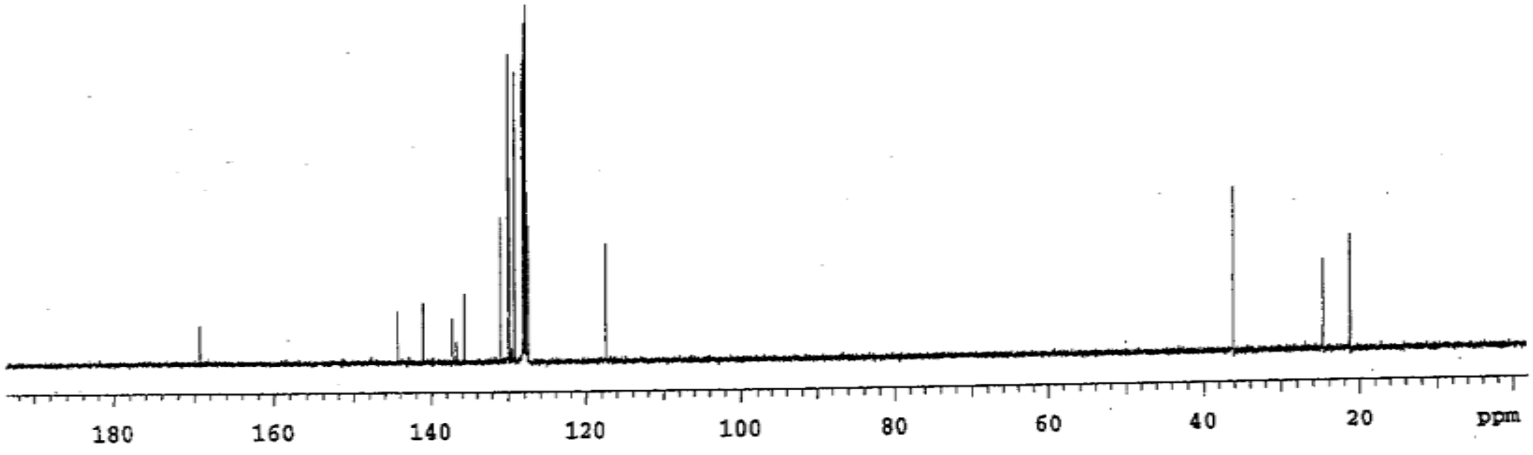

N
Ts
2. 94
^{13}C NMR, 125 MHz, C_6D_6
180
160
140
120
100
80
60
40
20
ppm

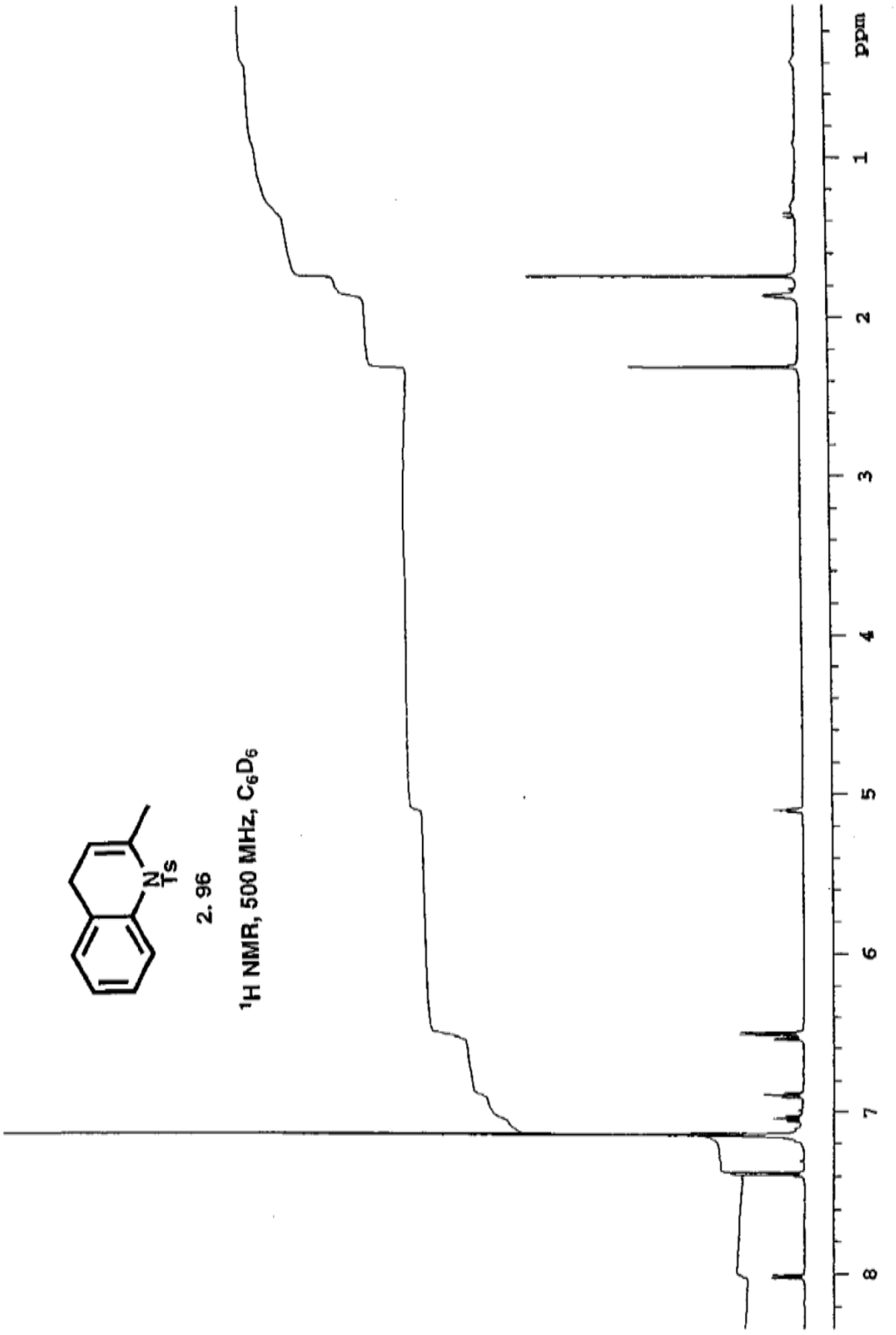

O
N
Ts
2. 95
^{1}H NMR, 500 MHz, C_6D_6
ppm
1
2
3
4
5
6
7
8

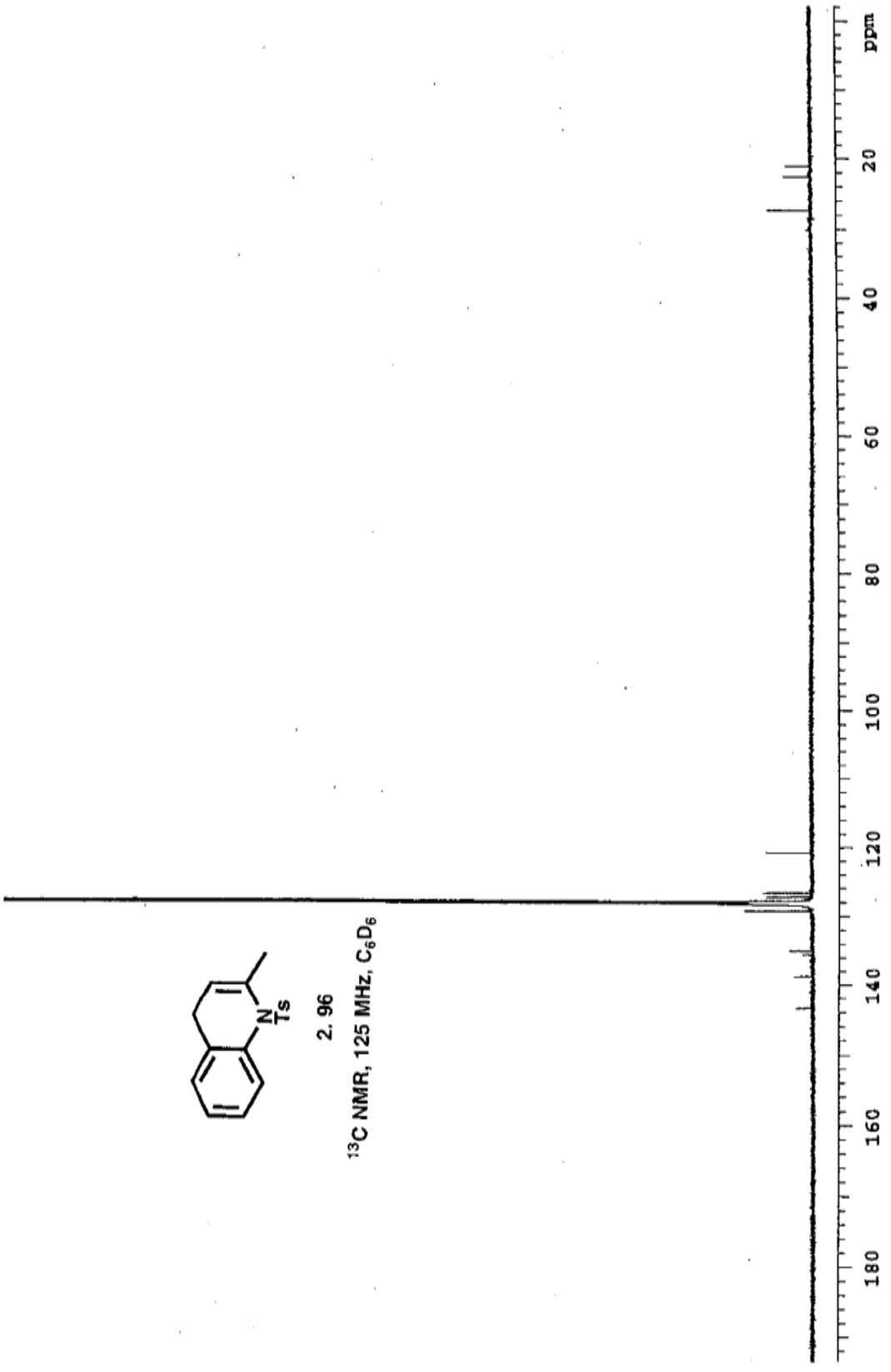


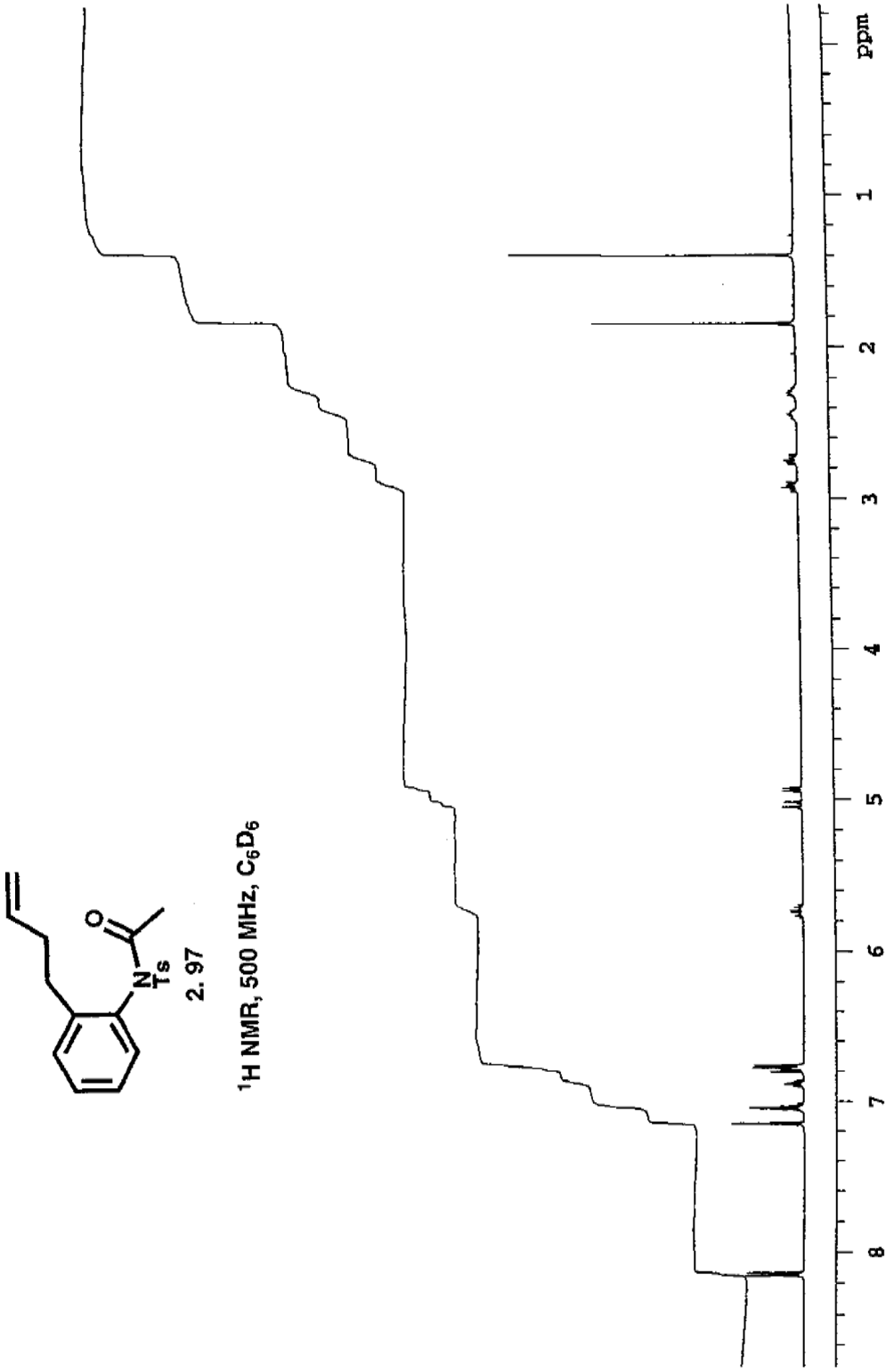
2. 95

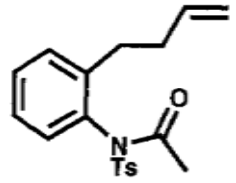
^{13}C NMR, 125 MHz, C_6D_6




2. 96
^{1}H NMR, 500 MHz, C_6D_6
Ts
N
ppm
1
2
3
4
5
6
7
8

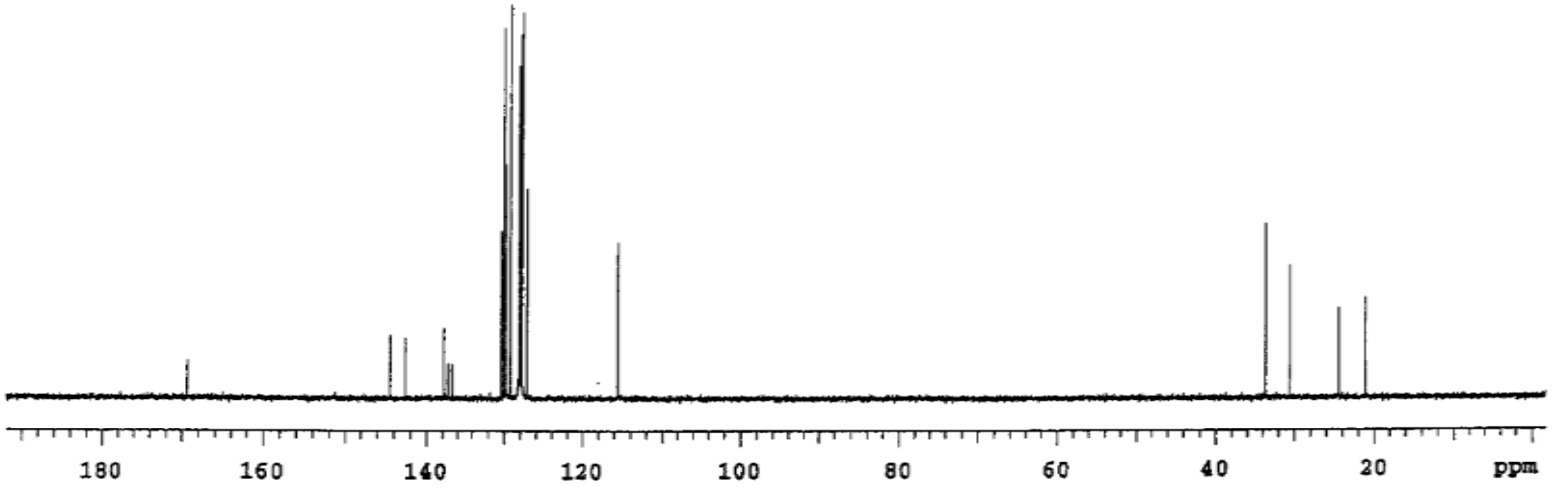

N
Ts
2. 96
^{13}C NMR, 125 MHz, C_6D_6
ppm
180
160
140
120
100
80
60
40
20

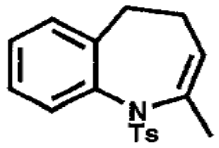

O
N
Ts
2. 97
^{1}H NMR, 500 MHz, C_6D_6
ppm
1
2
3
4
5
6
7
8



2. 97

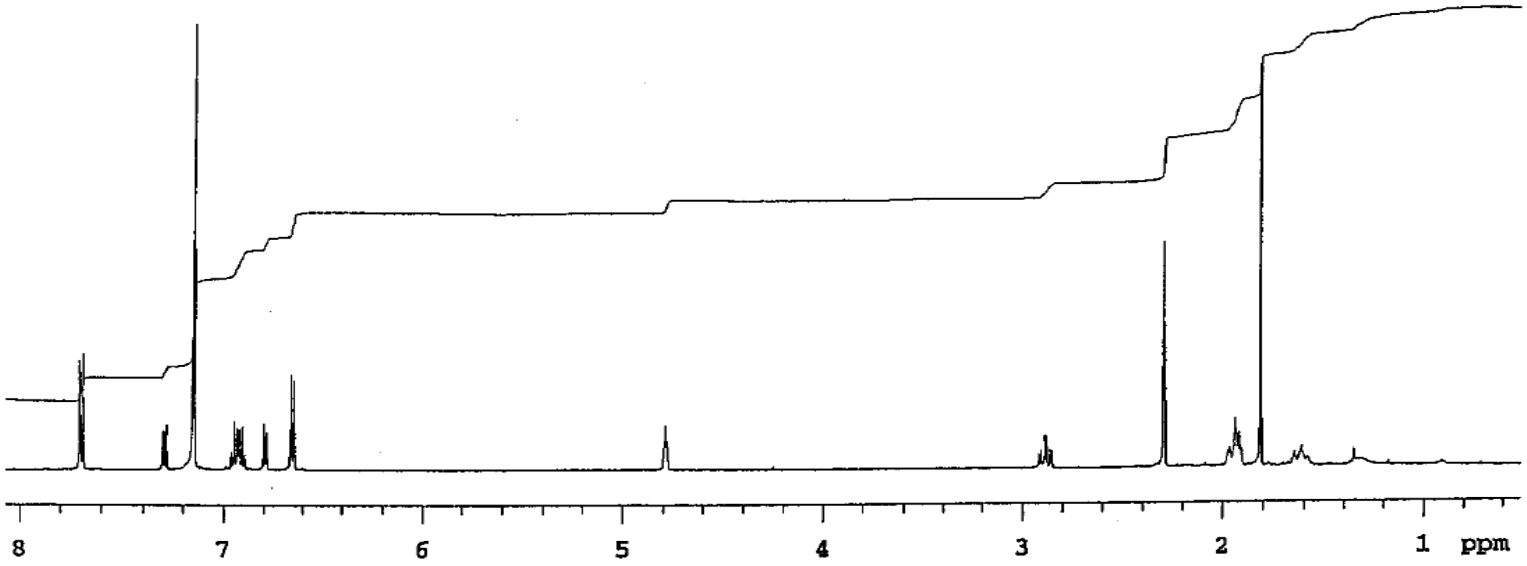
^{13}C NMR, 125 MHz, C_6D_6

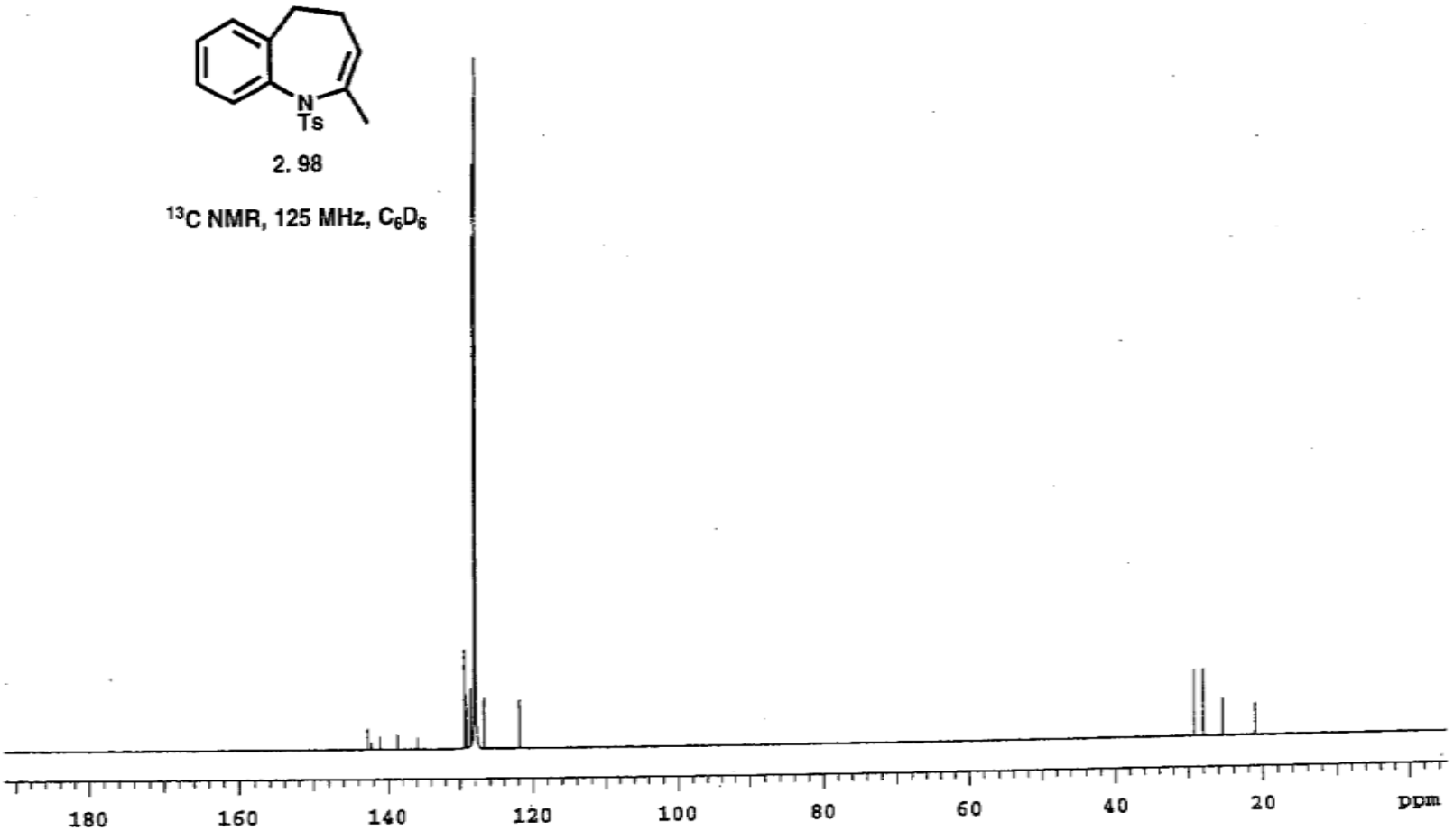


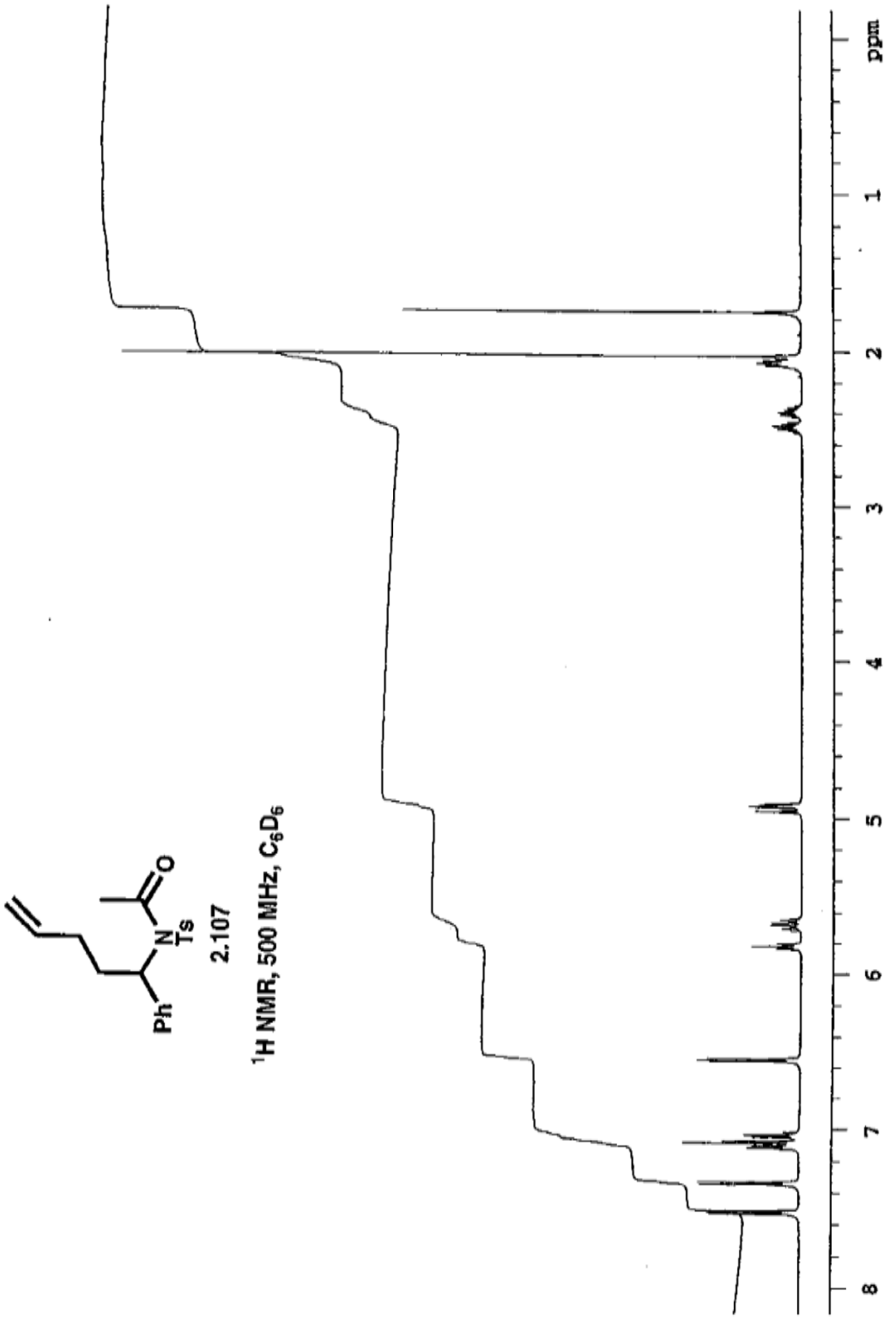


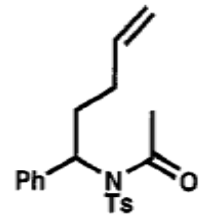
2. 98

^{1}H NMR, 500 MHz, C_6D_6



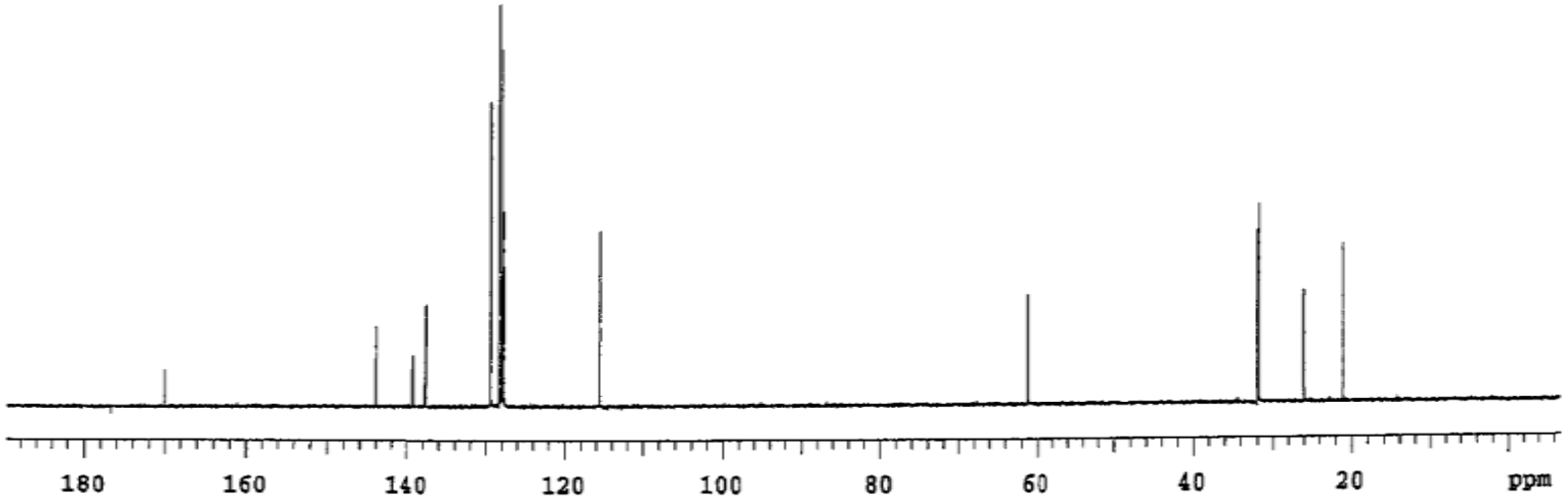

N
Ts
2. 98
^{13}C NMR, 125 MHz, C_6D_6
180
160
140
120
100
80
60
40
20
ppm

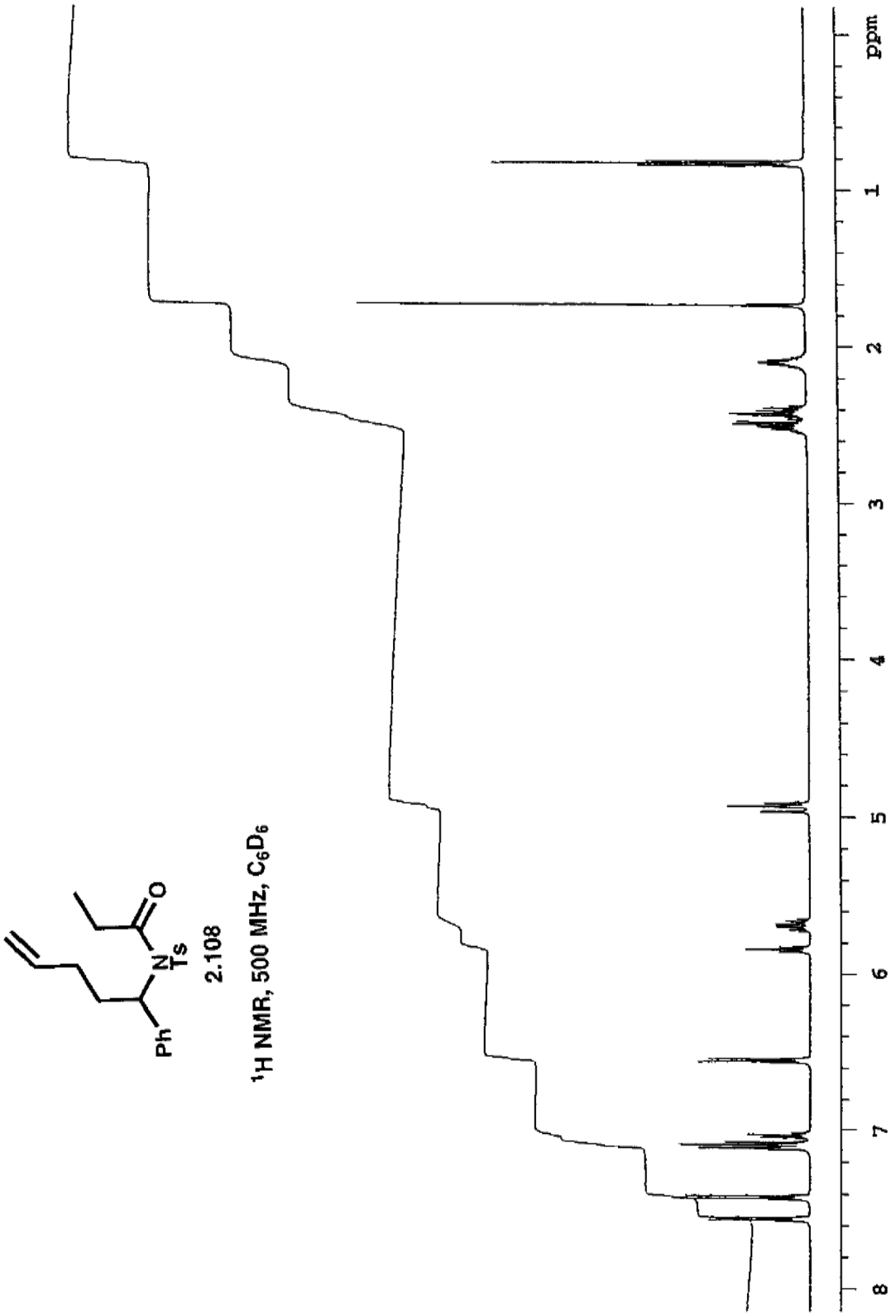

Ph
N
Ts
O
2.107
^{1}H NMR, 500 MHz, C_6D_6
ppm
1
2
3
4
5
6
7
8

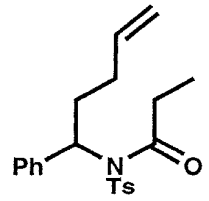


2.107

^{13}C NMR, 125 MHz, C_6D_6

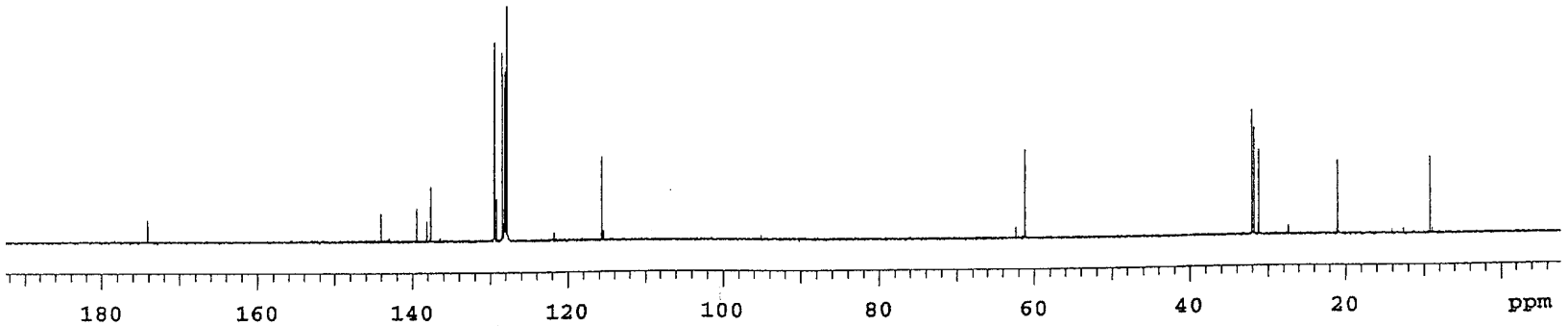


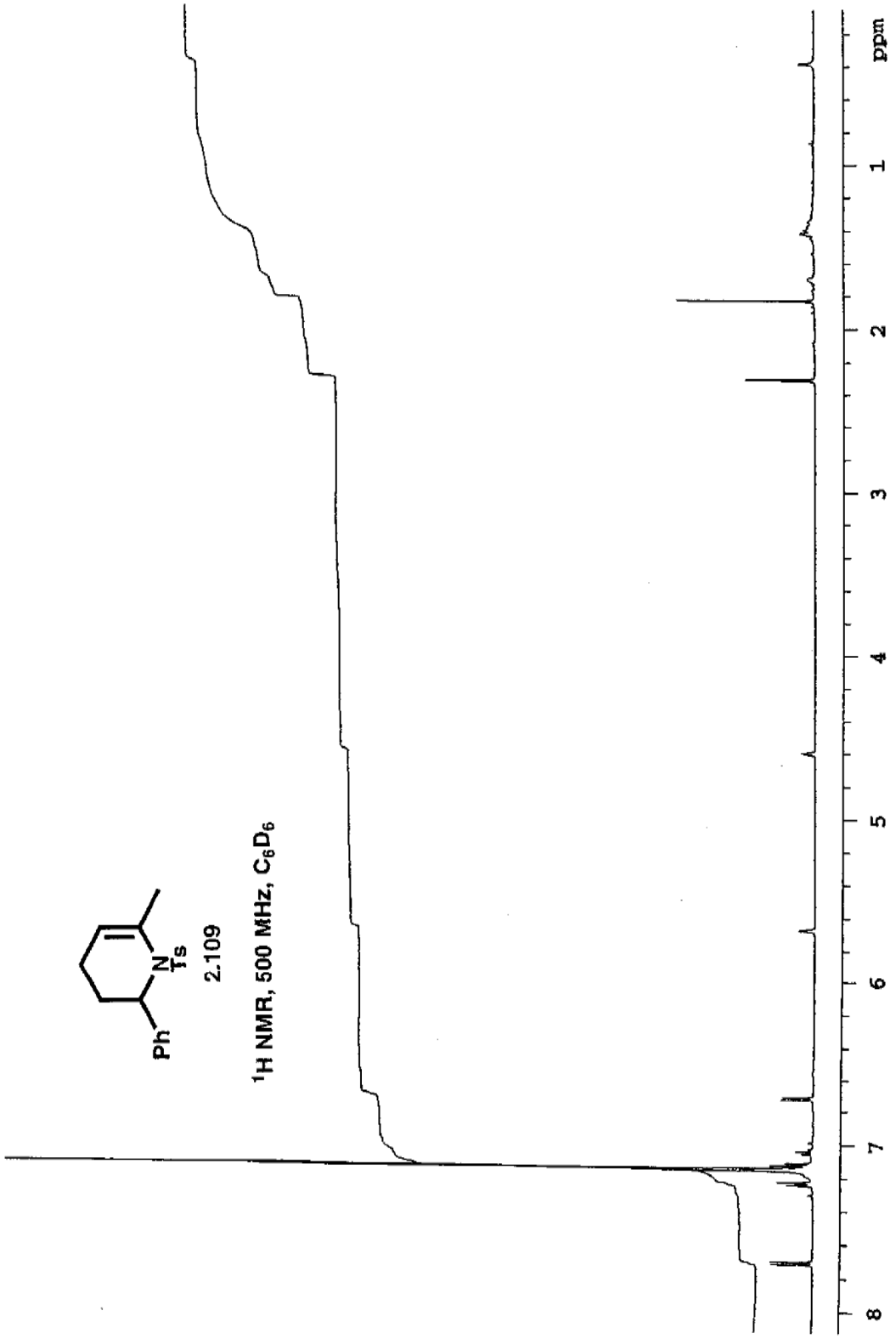

Ph
N
Ts
O
2.108
^{1}H NMR, 500 MHz, C_6D_6
ppm
1
2
3
4
5
6
7
8

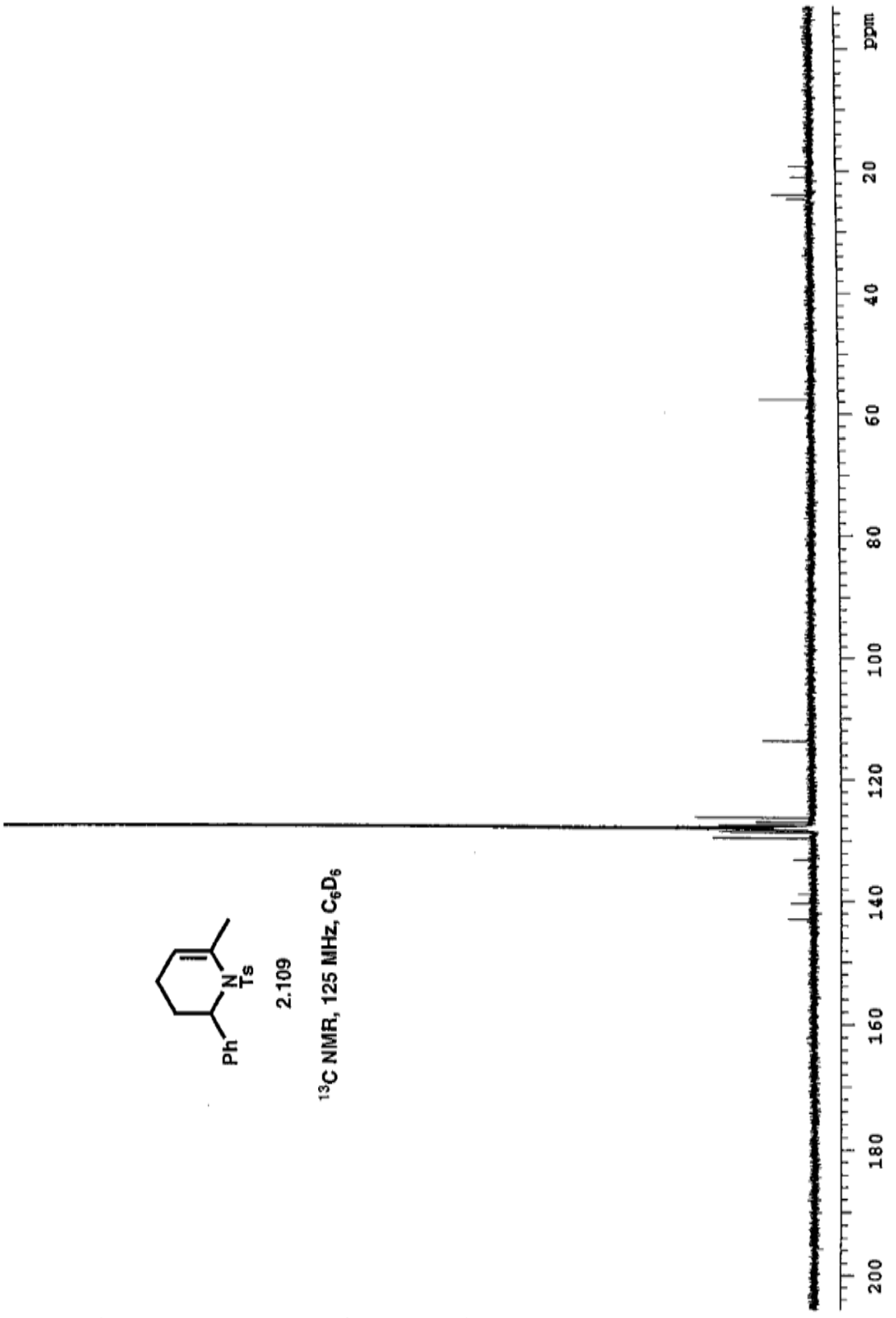


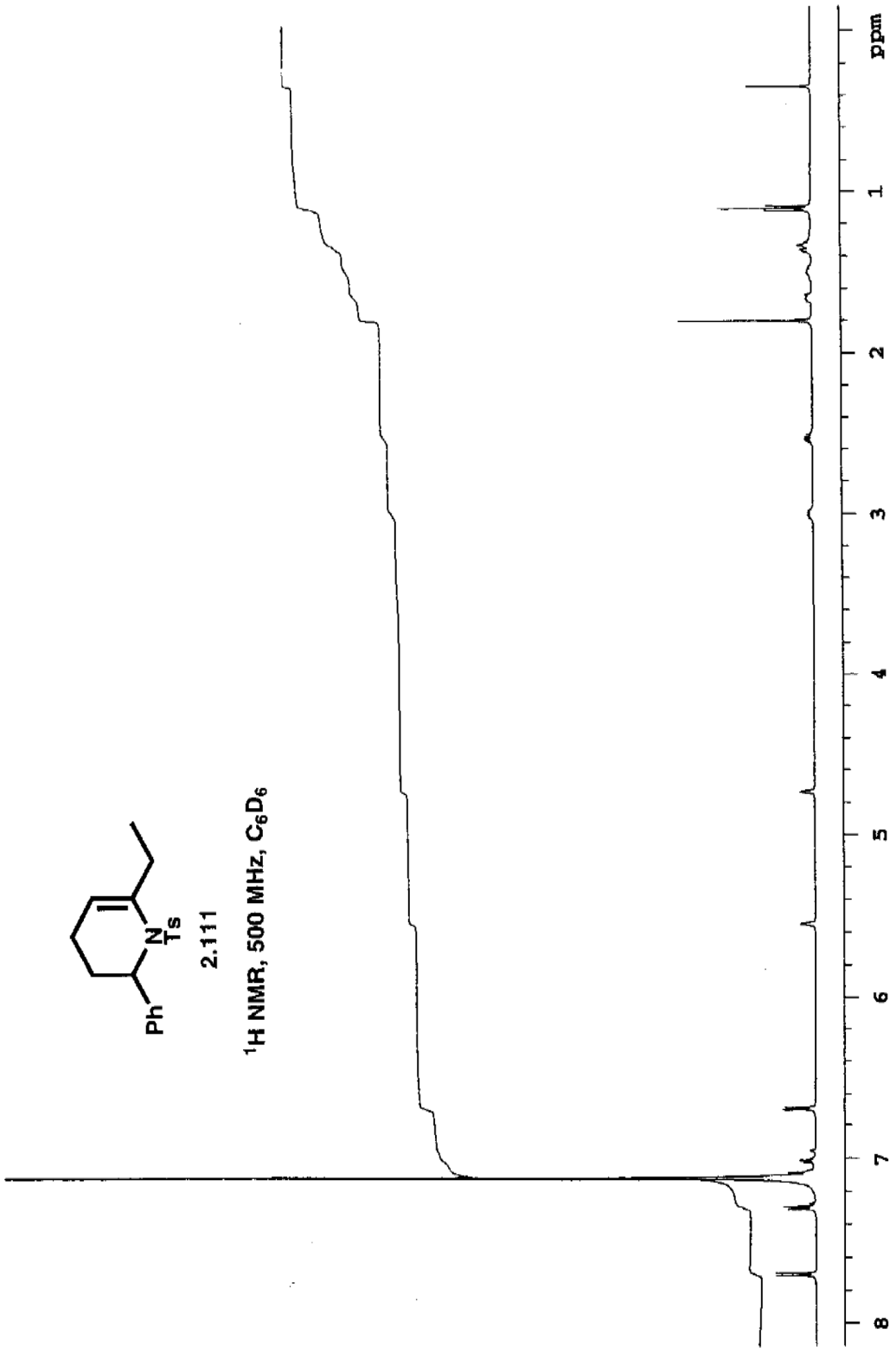
2.108

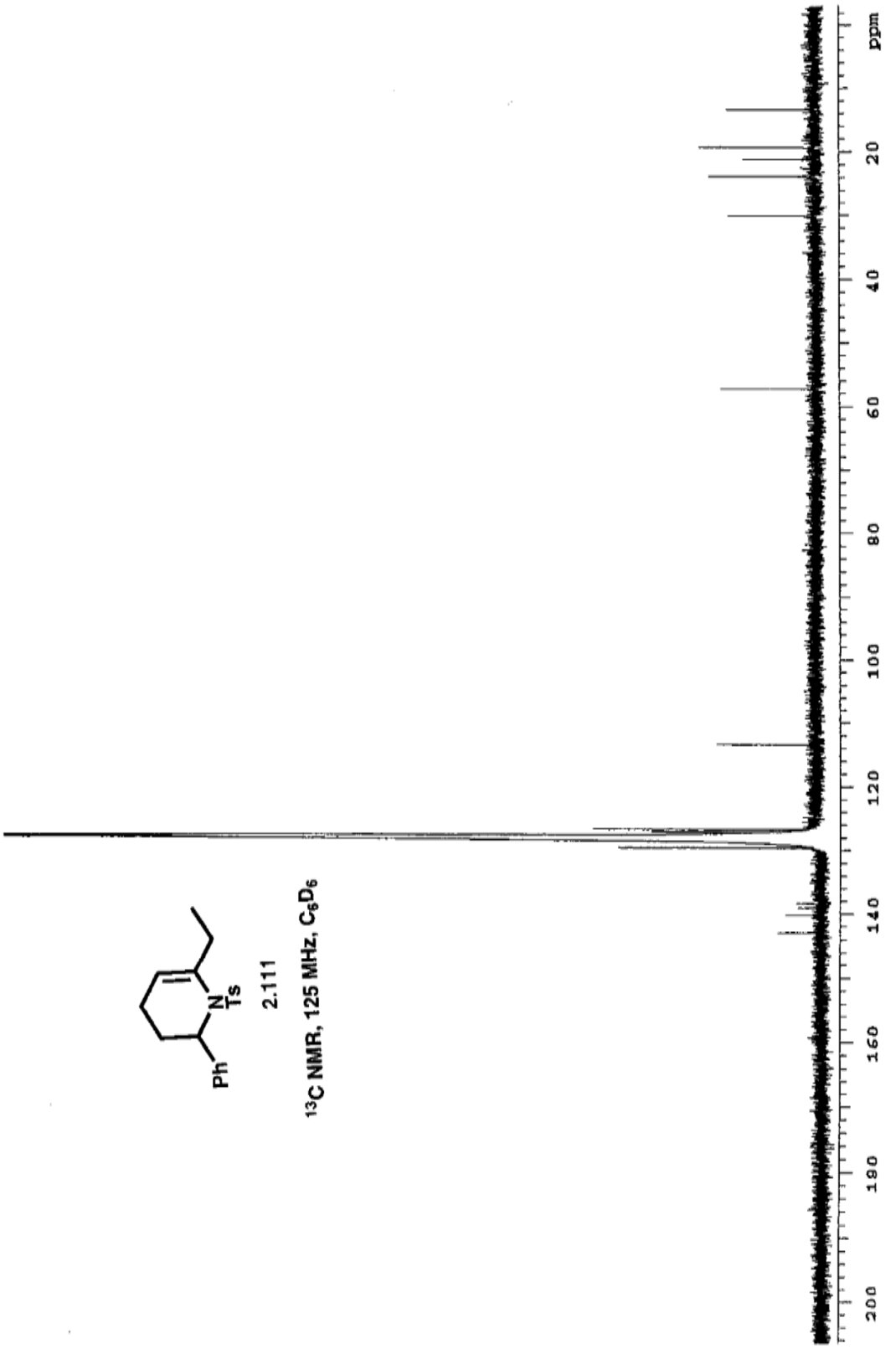
^{13}C NMR, 125 MHz, C_6D_6

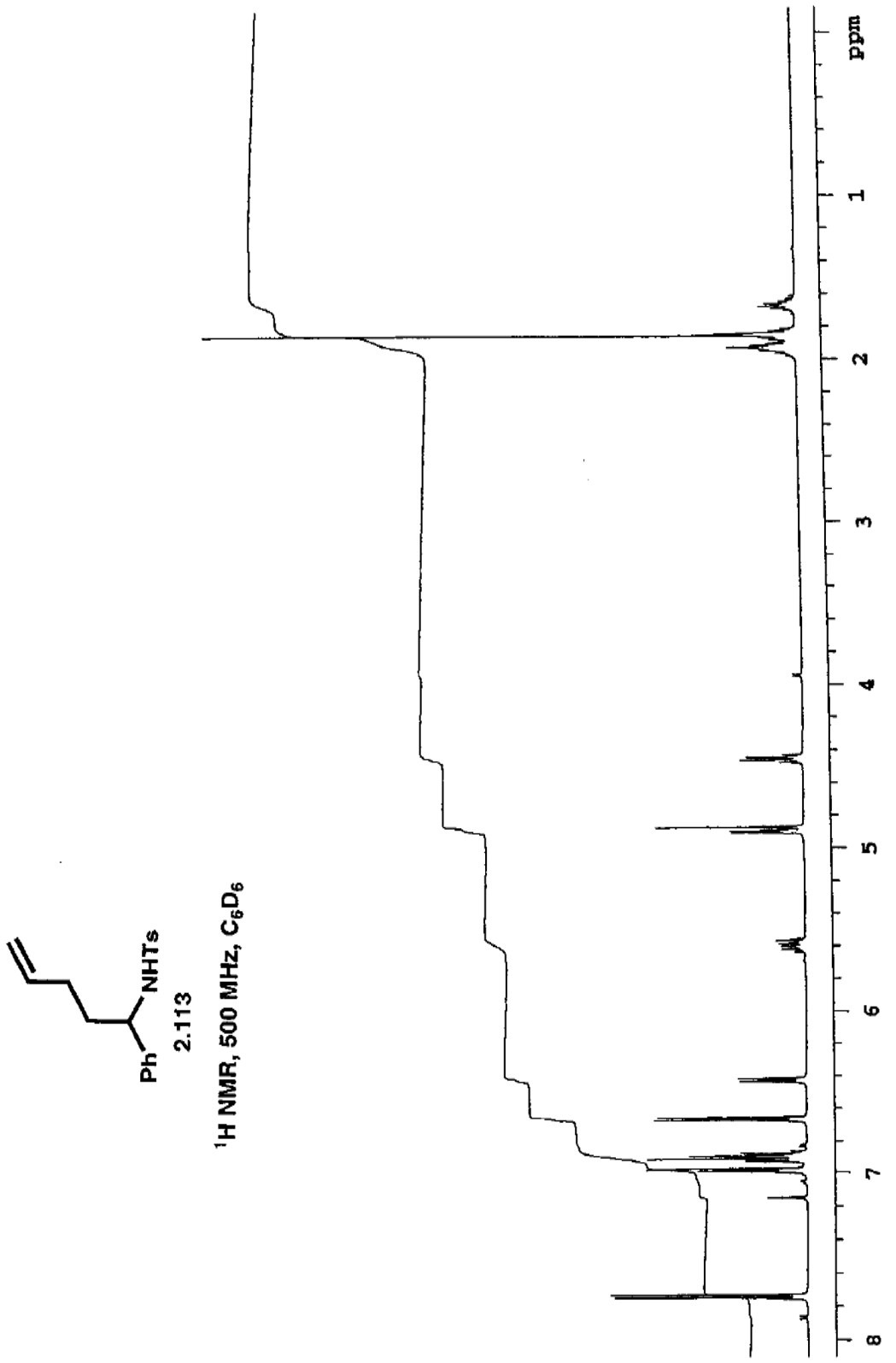


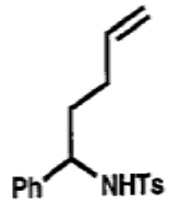

Ph
N
Ts
2.109
^{1}H NMR, 500 MHz, C_6D_6
ppm
1
2
3
4
5
6
7
8


Ph
N
Ts
2.109
^{13}C NMR, 125 MHz, C_6D_6
200
180
160
140
120
100
80
60
40
20
ppm


Ph
N
Ts
2.111
^{1}H NMR, 500 MHz, C_6D_6
8
7
6
5
4
3
2
1
ppm


Ph
N
Ts
2.111
^{13}C NMR, 125 MHz, C_6D_6
200
180
160
140
120
100
80
60
40
20
ppm


Ph
NHTs
2.113
^{1}H NMR, 500 MHz, C_6D_6
ppm
1
2
3
4
5
6
7
8



2.113

^{13}C NMR, 125 MHz, C_6D_6